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ORIGINAL ARTICLES

COMBINED USE OF ANGIOCARDIOGRAPHY AND CARDIAC CATHETERIZATION IN THE DIAGNOSIS OF CONGENITAL ANOMALIES OF THE CARDIOVASCULAR SYSTEM

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CARDIAC catheterization and angiocardiography are two established methods of investigation of congenital anomalies of the heart and great vessels. Each has a useful place in the task of elucidating the anatomic and physiologic complexities of cardiac malformations. While it is often possible, because of the brilliant studies of Dr. Helen Taussig,[1] to select suitable operative cases following a clinical evaluation, there are many problems requiring further study, and the use of these additional procedures. The purpose of this paper is to illustrate the manner in which each procedure may complement the other.

Catheterization follows the standard technic devised by Cournand and Ranges,[2] and estimation of blood flows is based on the "Fick principle" formulae elaborated by Bing.[3,4] The technic in angiocardiography has been described by Castellanos[5] and by Robb and Steinberg.[6] Seventy percent diodrast is the contrast medium used. A rapid X-ray film changer devised by Neuhauser[7] permits taking a film each 1½ sec. In 18 recent cases, catheterization has been followed by an angiocardiogram. There has been no indication that the risk of either procedure is thereby increased. Following completion of the catheterization, the catheter is withdrawn and a wide bore cannula is tied into the vein in readiness for the injection of dye. In 51 injections of 70% diodrast in 33 patients, no untoward reaction has as yet been experienced.

Angiocardiography may provide visual evidence of the relationship and size of cardiac chambers and great vessels, and in the serial X-ray films taken after the dye is injected

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it may be possible to follow the abnormal course of the intracardiac circulation in cardiac malformations. With cardiac catheterization it is possible to know the intracardiac pressures, to estimate the pulmonary arterial and systemic blood flows and the direction and quantity of abnormal shunts. From the course of the catheter and the determination of oxygen values additional information may be obtained regarding the intracardiac abnormalities.

It is important in the selection of cyanotic children who may be suitable for surgical therapy to have information regarding the point of origin, size, the intravascular pressure of and the amount of blood flowing through the great vessels particularly in the case of the pulmonary artery. The first three cases are presented to illustrate the type of problem which may arise, and the manner in which the combined use of the procedures in

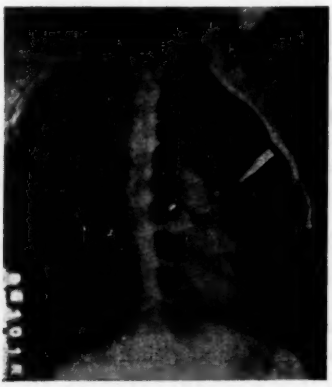

FIG. 1

FIG. 2

FIG. 1. Case 1—RAO projection. Prominence in the region of conus (arrow).

FIG. 2. Case 1—Angiocardiogram in LAO projection 2 sec. after dye injection. Simultaneous filling of aorta and pulmonary artery. Left pulmonary artery (upper arrow) is much larger than normal. Lower arrow points toward an unopacified area. (Compare with similar area shown in Fig. 7. Discussion in the text).

question may elucidate the problem. The diagnosis in the fourth case is not entirely clear, but it is considered worthy of presentation because it provides a good example of the way in which the data obtained by angiocardiography and cardiac catheterization may be utilized.

The first three patients whose cases are considered below were children between the ages of six and 15 years, all of whom had a markedly restricted exercise tolerance. They were cyanotic and had clubbing of fingers and toes. Each had a harsh systolic murmur of moderate (grade 3) intensity, maximal at the left sternal border in the third intercostal space. In each a thrill was palpable. A considerable degree of polycythemia was present in each patient. Electrocardiographic study showed a right axis deviation with evidence of right ventricular hypertrophy in the unipolar precordial leads.

CASE REPORTS

Case I was thought to be an instance of the tetralogy of Fallot with a right aortic arch. A question was raised as to the validity of this diagnosis by the X-ray and fluoroscopic demonstra-

TABLE I

CASE 1. DATA OBTAINED AT CARDIAC CATHETERIZATION

R.T.

Surface area — .71 m²
Oxygen consumed—154cc/min.

	Oxygen Vol. %	Pressure mm Hg.
Femoral artery	19.9	
Capacity	25.6	
% Saturation	77.7%	
S.V.C.	15.4	7
R.A. at tricuspid	16.4	7
R.V.	16.7	60
R.V.	15.7	60

Pulmonary artery flow—2026 cc/min.
Systemic flow —4400 cc/min.
Shunt R to L —2374 cc/min.

tion of the prominence of the quietly pulsatile conus region, best seen in the RAO view (Fig. 1), and further investigation was thought to be indicated. The catheter was introduced into the right ventricle, in which the pressure was greatly elevated, but it could not be passed into the pulmonary artery. Table I shows findings consistent with a tetralogy—a reduced pulmonary arterial blood flow in relation to the systemic output, and a large R-L shunt. The angiocardiogram (Fig. 2), on the other hand, revealed a surprisingly large left pulmonary artery. On the basis of these data, it was evident that there was present a pulmonary stenosis and post-stenotic dilatation of the left pulmonary artery. The right pulmonary artery was also somewhat larger than anticipated. A successful anastomosis between the left subclavian and left pulmonary artery was performed by Dr. Dudley E. Ross. The left pulmonary artery in this eight-year-old, 15 kg. patient

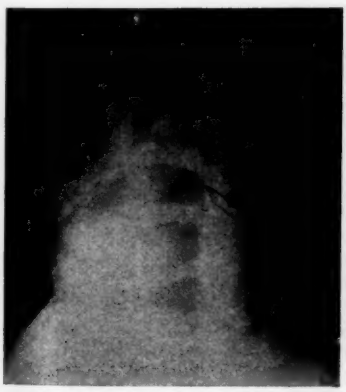

FIG. 3

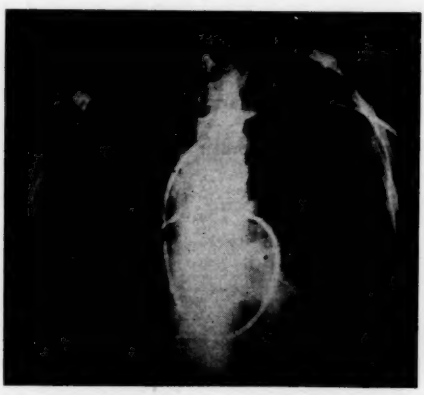

FIG. 4

FIG. 3. Case 2—Angiocardiogram in LAO projection 2 sec. after dye injection. Simultaneous filling of aorta and pulmonary artery. Note large size of latter vessel (arrow).

FIG. 4. Case 2—Cardiac catheterization. Catheter has passed through the pulmonary stenosis and tip lies in the descending branch of R pulmonary artery.

was as large as the surgeon's thumb but the pressure within it, measured at operation, was one sixth of that measured in the right ventricle at the time of catheterization.

Case 2, a 15-year-old-boy, was also considered to have a tetralogy of Fallot. However, on roentgenographic examination there was some prominence of the pulmonary arc in the PA and RAO projections. Furthermore, on two occasions the exercise test, as described by Bing,[3, 4] showed a rise in the ratio of oxygen consumed per liter of pulmonary ventilation, rather than the fall which usually occurs in the presence of a pulmonary stenosis. The angiocardiogram (Fig. 3) showed a large pulmonary artery and an over-riding aorta. Upon catheterization it was apparent, despite the demonstration of the large pulmonary artery, that there was a pulmonary stenosis. The catheter could be passed from the right ventricle either into the aorta or into the pulmonary artery (Fig. 4). Definite evidence of pulmonary stenosis was provided by the continuous strain gauge pressure recording as the catheter was withdrawn from the pulmonary artery back through the point of stenosis into the right ventricle (Fig. 5). The pressure in the pulmonary artery, 15/0

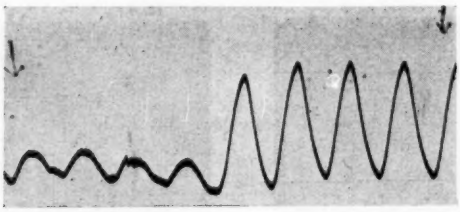

FIG. 5. Case 2—Cardiac catheterization. A continuous strain gauge pressure recording as catheter was withdrawn from the pulmonary artery in which pressure was 15/0 mm.Hg (L. portion of record) back into R ventricle where the pressure was 118/0 mm.Hg. This pressure relationship demonstrates presence of pulmonary stenosis.

TABLE II

CASE 2. DATA OBTAINED AT CARDIAC CATHETERIZATION

D.ST.D.

Surface area — 1.33 m²
Oxygen consumed—185cc/min.

	Oxygen Vol. %	Pressure mm Hg.
Femoral artery	23.0	
Capacity	29.8	
% Saturation	77.2%	
I.V.C.	19.9	
S.V.C.	19.1	
R.A.—upper	19.3	
R.A.—mid	20.6	
R.V.—upper	21.8	118/0
R.V.—mid	21.2	
R.V.—lower	20.5	
R. Pulmonary artery	21.3	15/0
Main Pulmonary artery	21.7	15/0
Aorta	24.2	115/75

Pulmonary artery flow—2108 cc/min/m²
Systemic artery flow —5795 cc/min/m²
Shunt—R to L —3687 cc/min/m²

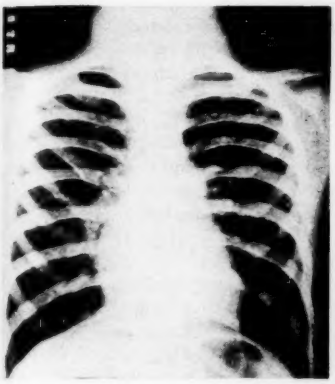

FIG. 6

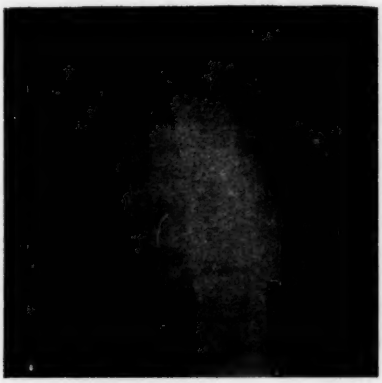

FIG. 7

FIG. 6. Case 3—Pulmonary artery is prominent and on fluoroscopy was actively pulsatile.

FIG. 7. Case 3—Angiocardiogram in PA projection 2 sec. after dye injection. There is simultaneous filling of aorta and pulmonary artery. Unopacified area, similar to that noted in Fig. 2, indicated by arrow.

mm.Hg, was greatly reduced as compared with the pressure of 118/0 mm.Hg in the right ventricle. Table II shows findings similar to those in Table I, Case 1—a large R-L shunt and a reduced pulmonary arterial blood flow in relation to the calculated systemic flow. A Blalock type of anastomosis was performed between the right subclavian and the right pulmonary artery. Shortly afterwards this patient experienced a fatal cerebral accident and at autopsy the findings of a tetralogy were demonstrated. The stenosis was in the outflow tract of the right ventricle and there was a large pulmonary artery.

Case 3 was considered to be an example of the Eisenmenger complex in view of the roentgenographic demonstration of the prominent, actively pulsatile pulmonary artery (Fig. 6), associated

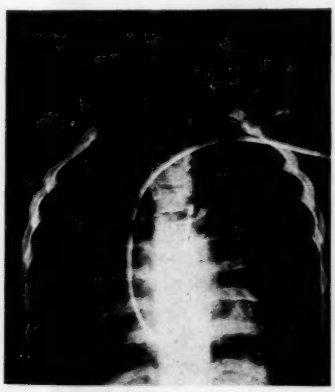

FIG. 8

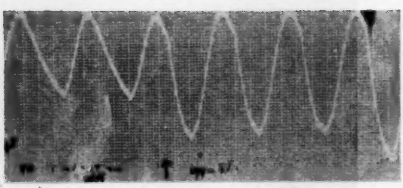

FIG. 9

FIG. 8. Case 3—Cardiac catheterization. Catheter tip lies in pulmonary artery.

FIG. 9. Case 3—Cardiac catheterization. Continuous strain guage pressure recording as catheter was withdrawn from pulmonary artery in which pressure was 50/15 mm.Hg (L. portion of record) back into R ventricle where pressure was 50/0 mm.Hg. No pulmonic stenosis.

with expansile pulsations in the hilar vessels. Because of the interest in this group of anomalies and because cases such as the preceding two had made us uncertain about the accuracy of ordinary methods in demonstrating the nature of the outflow tract of the right ventricle and pulmonary artery, the patient was subjected to further studies. The angiocardiogram (Fig. 7) revealed a large pulmonary artery and a small simultaneously-filled aorta. It is of interest to compare the angiocardiogram of Case 1 (Fig. 2) with that shown in Fig. 7. In both angiocardiograms there is a similar area, indicated by arrows, where there appears to be an absence of dye. The question has been raised as to whether this appearance signifies a region of stenosis, or whether it may be due to a cross-stream of left ventricular blood which, of course, would not contain diodrast. Data obtained at catheterization in this case demonstrated clearly that this area is not necessarily associated with stenosis. In the pulmonary artery (Fig. 8) the pressure was 50/15 mm.Hg and in the right ventricle it was 50/0 mm.Hg (Fig. 9).

The problem presented by Case 4 was the diagnosis of a middle mediastinal mass occurring in an eight-year-old Negro boy, with a history of a heart murmur from birth and moderate reduction in exercise tolerance. There was no cyanosis or polycythemia. The murmur was systolic in time and of moderate (grade 3) intensity. The electrocardiogram showed a right exis deviation with a pattern of right ventricular hypertrophy in the unipolar precordial leads. The mass was quietly pulsatile on fluoroscopic examination and appeared to be situated in the middle mediastinum

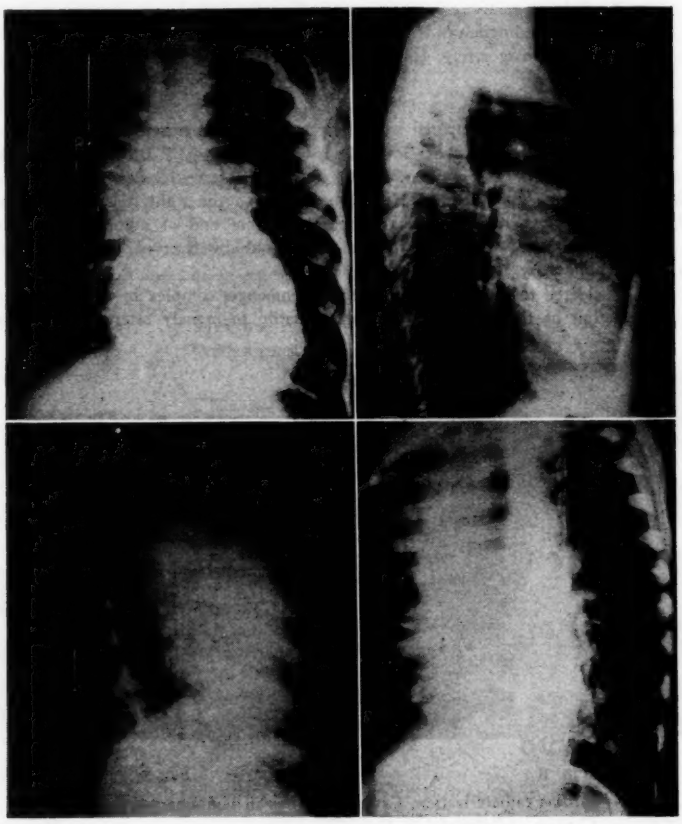

FIG. 10. Case 4—Mass is located in superior middle mediastinum. Upper left: PA; upper right: RL; lower left; RAO; lower right: LAO.

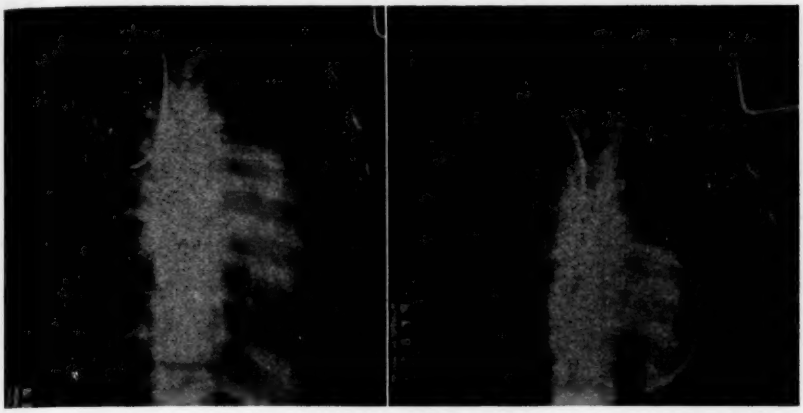

FIG. 11. Case 4—Cardiac catheterization. Left—catheter could be passed freely into R. portion of mass from the superior vena cava. Right—catheter passed freely into R. pulmonary artery and it was apparent that R portion of mass was not associated with the pulmonary artery or its branches.

(Fig. 10). The catheter is shown in two positions (Fig. 11). It could be passed freely into the pulmonary artery and it was evident that the right portion of the mass was not related to this vessel or its branches; or it could enter the right portion of the mass from the superior vena cava. This communication between the mass and the superior vena cava is well shown in the angiocardiogram (Fig. 12). The blood oxygen values (Table III) in the right portion of the mass, upper right auricle and right ventricle were significantly higher than samples taken from the inferior vena cava. It is apparent that blood from the arterial side was gaining access to the right heart. It was considered unlikely that an atrial septal defect, with blood flow from left to right atrium, could explain this finding because of the high oxygen value in the mass. However, the entry of one or more of the pulmonary veins into the superior vena cava could well be the anomaly which is associated with these findings. In the injection of dye (Fig. 13) done from the right saphenous vein in the thigh, the dye immediately passed across to the left border of the heart shadow. That it entered the left atrium through an opening in the atrial septum is probable, for a flow from right to left atrium, which contained a mixture of arterialized and venous blood, could offer an explanation for the small degree of unsaturation of the femoral artery blood.

In 1942 Brody[8] collected 102 cases from the literature in which postmortem examination revealed drainage of the pulmonary veins into the right side of the heart, and added four of his own. In 38 cases there was total drainage of the pulmonary veins into the right atrium or its branches and in 68 cases one or more, but not all, the pulmonary veins entered the right side. In this latter group there were 29 cases with drainage into the superior vena cava. In two of these there was an associated atrial septal defect, and in three the superior vena cava communicated partly with the right and partly with the left atrium.

It is suggested that our Case 4 shows evidence of pulmonary vein drainage into the superior vena cava. A striking feature is the association of this abnormality of drainage from the lung with the mass. The question is raised as to whether the mass represents an aneurysm of the superior vena cava or of a pulmonary vein, perhaps at the site of entry into the superior vena cava. No explanation can be offered for the left portion of the mass which has not been entered by dye or catheter. Although the diagnosis is unconfirmed,

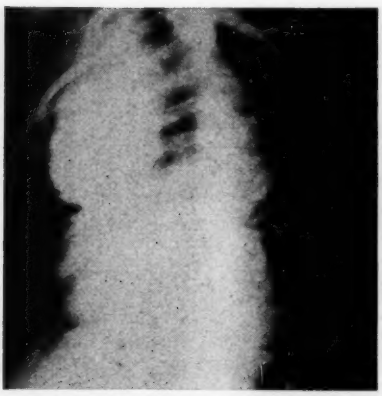

FIG. 12

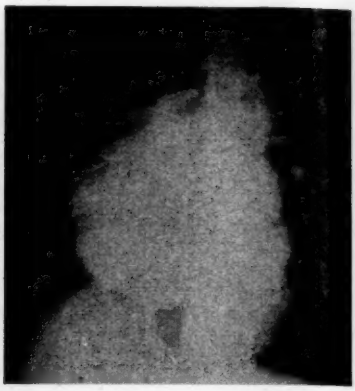

FIG. 13

FIG. 12. Case 4—Angiocardiogram in LAO projection 1 sec. after dye injection. Right portion of mass is well filled with dye from superior vena cava.

FIG. 13. Case 4—Angiocardiogram in LAO projection, 2 sec. after dye injection. Dye has passed across to L. border of heart.

the case well illustrates the way in which each method may contribute special data in a difficult diagnostic problem.

TABLE III

CASE 4. DATA OBTAINED AT CARDIAC CATHETERIZATION

	Oxygen Vol. %	Pressure mm. Hg.
Femoral artery	14.1	
Capacity	16.5	
% Saturation	85.4%	
I.V.C.	12.4	12
R.A.—lower	13.8	12
R.A.—upper	15.1	
Right portion of mass	15.1	15
R.V.—upper	15.4	28
R. pulmonary artery	15.3	20
R. pulmonary artery	15.6	20

SUMMARY

The findings of cardiac catheterization and angiocardiography in three cyanotic children with congenital anomalies of the heart and great vessels have been presented to demonstrate the value of these procedures, particularly in elucidating problems in connection with the pulmonary artery. In the fourth case of acyanotic cardiovascular disease the relationship between the two methods is further illustrated. No toxic reactions have occurred in 51 injections of 70% diodrast. Following a cardiac catheterization with an angiocardiogram does not appear to increase the risk of either procedure.

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Spanish Abstract

Uso Combinado de la Angiocardiografia y el Cateterismo Cardiaco en la Diagnosis de Anomalias Congenitas del Sistema Cardiovascular

El cateterismo cardiaco y la angiocardiografía son dos métodos establecidos de investigación en anomalías congénitas del corazón y los grandes vasos. Cada uno tiene un lugar útil en la explicación de las complexidades fisiológicas de las malformaciones. En casos donde se requieren ambos, hemos seguido el cateterismo cardiaco con un angiocardiograma. Después de que se retira el catéter, se amarra una cánula en la vena lista para inyectar el tinte.

El peligro de cualquiera de estos procedimientos no parece ser aumentado por eso.

Se presentan casos de niños cianóticos con anomalías cardiacas para ilustrar el uso de los dos métodos demostrando la naturaleza del tracto de salida del ventrículo derecho y la arteria pulmonar. Ha sido posible demostrar la estenosis pulmonar en asociación con la dilatación postestenótica. Se presenta un caso más de la masa mediastínica media. La porción derecha de la masa se llenó con tinte desde la vena cava superior y según los datos de cateterismo, es aparente que la sangre arterializada entraba en la masa. Por consiguiente esto indica que una o más venas pulmonares desaguan en la vena cava superior, y que la porción derecha de la masa es un aneurisma de la vena cava superior o de la vena pulmonar. El caso ilustra la manera en la cual los does procedimientos pueden contribuir datos especiales para un problema diagnóstico difícil de un niño cianótico con la malformación cardiovascular.

1615 Cedar Ave.

THE ABSORPTION OF OILY AND AQUEOUS PREPARATIONS OF ESTER AND ALCOHOL VITAMIN A BY NORMAL CHILDREN AND CHILDREN WITH VARIOUS DISEASES

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Rochester, N.Y.

FOR some years we have frequently used the oral vitamin A absorption test as an aid in the diagnosis and treatment of various diseases. Until about two years ago, the ester form of vitamin A, which is that present in fish liver oils, was employed in carrying out the tests. At that time Professor S .W. Clausen suggested that we compare the absorption of the ester and the alcohol or "predigested" form of vitamin A by children suffering from cystic fibrosis of the pancreas. We found that while these children absorbed very little ester vitamin A, they did absorb the alcohol vitamin A well. Both forms of the vitamin were dissolved in oil. This suggested that we compare the absorption of these preparations of vitamin A by normal infants, older children and adults and by patients suffering from various diseases.

This work was almost completed when our attention was called to the most interesting reports of Kramer, Sobel and Gottfried[1] and Lewis, Bodansky, Birmingham and Cohlan.[2] These authors concluded that aqueous preparations of alcohol vitamin A, when given by mouth, were absorbed strikingly better by normal children, adults and patients with certain diseases than ester vitamin A in oleum percomorphum. They based their conclusions to a considerable extent upon the concentration of vitamin A in the blood serum three hours after the ingestion of the vitamin A.

Their work suggested the following questions for further investigation: 1. After the ingestion of the test doses of oily and aqueous preparations of vitamin A, at what times are the maximum concentrations of vitamin A in the serum found? 2. How long does the concentration of vitamin A in the serum remain elevated after ingestion of the test doses? 3. How does the concentration of vitamin A in the preparations, and consequently the amount of dispersing medium ingested, affect the absorption of the vitamin? 4. How can the test dose be most quantitatively adminisered to the subjects? We have attempted to answer some of these quesions.

The results of these various studies are reported in this paper.

From the Department of Pediatrics, The University of Rochester School of Medicine and Dentistry, Rochester, N.Y.

Preliminary reports of this work were given before the Division of Biological Chemistry of the American Chemical Society, 112th meeting, September 15, 1947, New York City, N.Y., and 113th meeting, April 19, 1948, Chicago, Ill.

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Absorption of Oily Preparations of Ester and Alcohol Vitamin A by Normal Human Subjects

In our usual procedure for carrying out the vitamin A absorption test, a fasting blood specimen of about 5 ml. is obtained, and the subject is then given by mouth 7,000 I. U./kg. body weight of vitamin A. Specimens of blood are taken four and seven hours later and the concentration of vitamin A in the specimens of blood serum determined as has been described by Clausen, Baum, McCoord, Rydeen and Breese.[3] As is shown later in this paper, the maximum concentration of vitamin A in the serum is found four to five hours after ingestion of the oily preparations. During the test, the subject eats his usual meals, but vitamin A supplements are prohibited during the test and for one or two days preceding the test.

TABLE I

Absorption of Oily Preparations of Ester and Alcohol Vitamin A by Normal Subjects

Number of subjects	Test dose: 7,000 I.U./kg. body weight vitamin A by mouth											
	Ester vitamin A						Alcohol vitamin A					
	Mean I.U. vitamin A per 100 ml. serum											
	Fasting	P. E.	4 Hours after vitamin A	P. E.	7 Hours after vitamin A	P. E.	Fasting	P. E.	4 Hours after vitamin A	P. E	7 Hours after vitamin A	P. E.
Normal infants 4 hours-10 days old 13♂, 22 ♀	76	6	502	46	—	—	95	7	688	80	—	—
Older children 7♂, 6 ♀	148	10	1,569	175	616	58	122	11	817	99	676	122
Normal adults 3♂, 9 ♀	137	7	1,300	129	642	95	118	7	1,273	194	752	95

We first compared the absorption of ester and alcohol vitamin A by 13 normal male and 22 normal female infants, aged four hours to ten days. After the fasting sample of blood was taken, the infant's mouth was opened wide and the required dose of vitamin A dropped far back on its tongue. We used oils* which contained 210,000 I. U/gm. vitamin A and the droppers used delivered 50 drops/gm. of oil. As we wished to avoid withdrawing too much blood from the infant, a single specimen of blood was obtained four hours after ingestion of the vitamin A.

Half of the babies received the ester vitamin A test first, followed by the alcohol vitamin A test two to four days later, while the remaining half received the alcohol vitamin A test first. None of the mothers had been given vitamin A supplements previous to the birth of the baby. The results of the vitamin A analyses for the infants are shown in Table I.

In a similar manner we studied the absorption of the two forms of vitamin A by seven convalescent boys and six girls, aged three to 14 years. From their clinical records, we

* The ester vitamin A was obtained from Abbott Laboratories, North Chicago, Ill., and the alcohol vitamin A from The Borden Vitamin Company, New York City, N.Y.

considered that their vitamin A absorption curves should be the same as those of normal children. The values obtained for these children are also shown in Table I.

The normal adult group included three men and nine women, who were doctors, medical students or persons employed in the Strong Memorial Hospital. The values found in their tests are also given in Table I. For the older children and adults, the required test dose of vitamin A in oil was placed in small gelatin capsules which the subjects swallowed without complaint.

The ability of the newborn infants to absorb vitamin A was very variable; some infants absorbed almost none of the test dose of either the ester or alcohol vitamin A, while others absorbed one or both forms excellently, as is shown in Table II. Neither the age of the child nor the order in which the ester and alcohol vitamin A tests were given seemed to affect the absorption; for example, infant SC was only four hours old at the time the ester test was done.

TABLE II

ABSORPTION OF OILY PREPARATIONS OF ESTER AND ALCOHOL VITAMIN A BY NORMAL NEWBORN INFANTS

Test dose: 7,000 I.U./kg. body weight vitamin A by mouth

Infant	Ester vitamin A		Alcohol vitamin A	
	I.U. vitamin A/100 ml. serum			
	Fasting	4 Hours after vitamin A	Fasting	4 Hours after vitamin A
DO	65	141	141	144
SH	84	114	65	122
SC	106	1,467	274	437
GE	15	984	38	125
RD	84	103	224	1,159
RE	103	129	114	1,953
LA	205	1,474	190	2,375
DE	167	794	19	2,933

The mean four hour value for the infant ester series was 502 I. U., and for the alcohol series, 688 I. U., the coefficient of correlation between the two values being +0.227. This indicates that many of the children who absorbed ester vitamin A well absorbed alcohol vitamin A well also. For the older convalescent boys and girls, the mean four hour value for the ester series was 1,569 I. U., and for the alcohol series, 817 I. U., the coefficient of correlation being −0.444. This indicates that many of the children absorbed one form of vitamin A much better than the other, although they really assimilated both forms very well. For the normal adults, the mean four hour value in the ester series was 1,300 I. U., and in the alcohol series, 1,273 I. U., the coefficient of correlation being +0.422, which signifies that most of the subjects absorbed both forms of the vitamin about equally well.

ABSORPTION OF OILY PREPARATIONS OF ESTER AND ALCOHOL VITAMIN A BY CHILDREN WITH CYSTIC FIBROSIS OF THE PANCREAS

The comparison of the absorption of the oily preparations of ester and alcohol vitamin A has proved most useful in the diagnosis of 13 cases of cystic fibrosis of the pancreas.

The ages of the children ranged from two months to 12 years at the time a diagnosis of cystic fibrosis of the pancreas was definitely established. Many of the children had suffered from failure to gain weight, frequent upper respiratory infections, bronchitis, pneumonia and bouts of diarrhea almost since birth. In these patients, the glucose tolerance curves were sometimes flat though more often normal. When the children received a normal diet, the stool fat, which was often only partly split, was elevated, being more than 33% of the dry weight of the stool or more than 3 gm. per day. In the juice obtained from the duodenum, trypsin and amylase were either absent or present in very low concentrations; lipase activity was not determined. Fluoroscopic and X-ray examinations sometimes showed infiltration and other changes in the lungs, but were frequently not helpful in establishing the diagnosis. In one case the diagnosis was confirmed at autopsy.

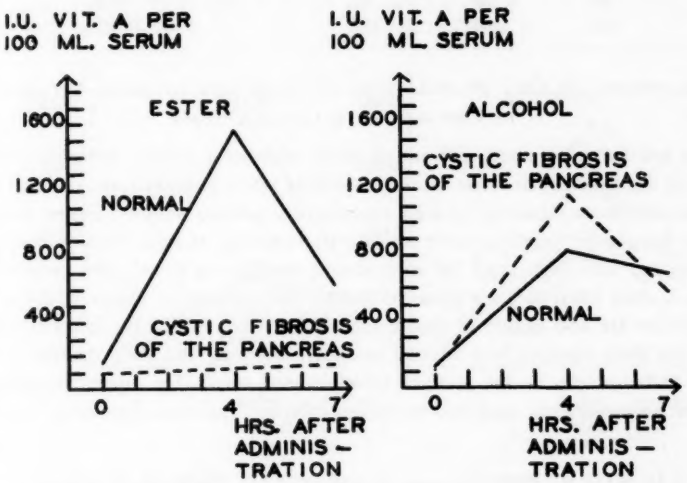

FIG. 1. Vitamin A absorption curves representing mean concentrations of vitamin A in serum of 13 normal children and of 13 children with cystic fibrosis of the pancreas after an oral test dose of 7,000 I.U./kg. body weight of ester or alcohol vitamin A in oil.

As is shown in Figure 1, children with cystic fibrosis of the pancreas absorbed the ester vitamin A very poorly, but the alcohol vitamin A very well. The curves shown in the figure represent mean values for the 13 patients; the mean four hour value for the ester series was 126 ± 67 I. U., and for the alcohol series, $1,149 \pm 1,109$ I. U. The normal vitamin A absorption curves shown in Figure 1 are plotted from the data for the older boys and girls given in Table I.

The pancreas of the children with cystic fibrosis of the pancreas cannot form the enzymes necessary for the intestinal digestion of fats, proteins and carbohydrates. As is shown in Table III, some of these patients absorbed ester vitamin A in oil well when it was given by mouth with Pancreatin, a commercial preparation which contains the pancreatic enzymes.

It is of interest that a 56-year-old man who had been subjected to excision of the duodenum and head of the pancreas because of adenocarcinoma of the ampulla of Vater absorbed the ester vitamin A poorly, but the alcohol vitamin A well.

TABLE III

EFFECT OF PANCREATIN ON THE ABSORPTION OF ESTER VITAMIN A IN OIL BY PATIENTS WITH CYSTIC FIBROSIS OF THE PANCREAS

Patient	Test dose: 7,000 I.U./kg. body weight, vitamin A by mouth					
	Ester vitamin A			Ester vitamin A+1 gm. Pancreatin		
	I.U. vitamin A/100 ml. serum					
	Fasting	Hours after vitamin A		Fasting	Hours after vitamin A	
		4	7		4	7
HU	49	53	76	91	578	236
LA	103	141	167	178	927	771

ABSORPTION OF OILY PREPARATIONS OF ESTER AND ALCOHOL VITAMIN A BY CHILDREN WITH CELIAC DISEASE

It has sometimes been very difficult to decide whether a child is suffering from cystic fibrosis of the pancreas or celiac disease, especially when a satisfactory specimen of juice from the duodenum cannot be secured. Occasionally patients with the former disease also have the flat glucose tolerance curve which is characteristic of celiac disease. Both diseases are associated with high stool fat content and inability to absorb oily preparations of vitamin A ester when they are given by mouth. As is shown in Figure 2, children with celiac disease are also unable to absorb the alcohol vitamin A. This is what one would expect, for these patients have normal intestinal enzymes, and their inability to absorb fat and carbohydrates is due to some undetermined cause. The curves represent mean values for seven patients, aged two months to 16 years. The mean four hour value for the

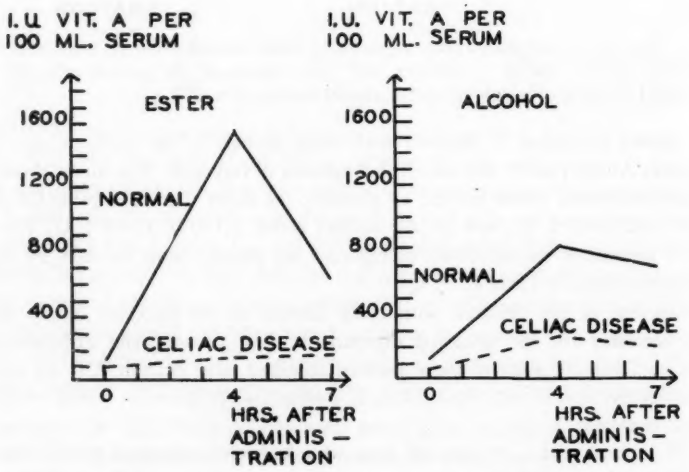

FIG. 2. Vitamin A absorption curves representing mean concentrations of vitamin A in serum of 13 normal children and of seven children with celiac disease after an oral test dose of 7,000 I.U./kg. body weight of ester or alcohol vitamin A in oil.

ester series was 142 ± 98 I. U., and for the alcohol series, 256 ± 203 I. U. Two adults suffering from steatorrhea absorbed little of these ester or alcohol preparations of vitamin A.

Absorption of Oily Preparations of Ester and Alcohol Vitamin A by Children with Anemia, Diarrhea, Giardiasis and Severe Malnutrition

In Figure 3 are shown the ester and alcohol vitamin A absorption curves representing mean values obtained for seven patients with quite severe anemia (AN). There were two cases of hypochromic anemia, and one case each of microcytic anemia, macrocytic anemia, congenital hemolytic anemia, erythroblastosis fetalis neonatorum, anemia associated with dwarfism, and anemia associated with chronic arthritis; five patients with

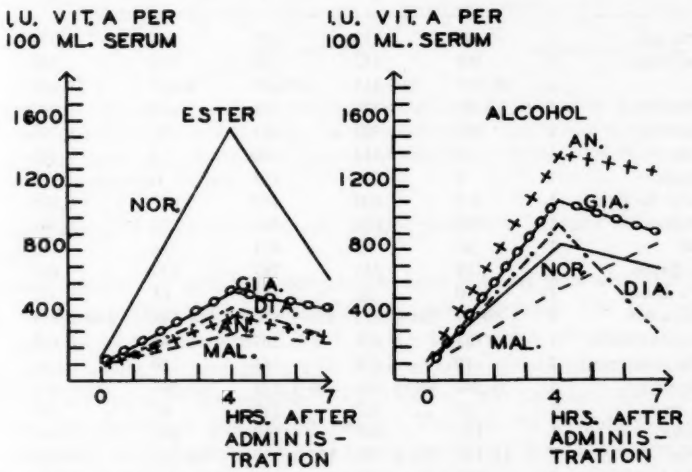

FIG. 3. Vitamin A absorption curves representing mean concentrations of vitamin A in serum after an oral test dose of 7,000 I.U./kg. body weight of ester or alcohol vitamin A in oil. The subjects were: 13 normal children (NOR); five patients with giardiasis (GIA); five patients with diarrhea (DIA); seven patients with anemia (AN); eight patients with severe malnutrition (MAL).

diarrhea (DIA); five patients with giardiasis (GIA); eight patients suffering from severe malnutrition (MAL). Each class of patients did not absorb the ester vitamin A as well as normal children and did absorb the alcohol vitamin A much better than the ester. However, since it is considered that if the four hour value is as much as 400 I. U., the absorption of vitamin A is within low normal limits, only patients with severe malnutrition may possibly develop vitamin A deficiency.

Absorption of Oily Preparations of Ester and Alcohol Vitamin A by Patients with Various Diseases

In Table IV are shown the ester and alcohol vitamin absorption tests of patients suffering from various diseases. All except five of these patients were children. The four and seven hour values obtained for the subjects were very variable, and there seemed to be a tendency for children who had been routinely receiving generous vitamin A supplements before admission to the hospital to have the higher values. There also seemed to be a tendency for children suffering from an acute illness to absorb the alcohol vitamin A better than the ester.

TABLE IV

ABSORPTION OF OILY PREPARATIONS OF ESTER AND ALCOHOL VITAMIN A BY PATIENTS WITH VARIOUS DISEASES

Test dose: 7,000 I.U./kg. body weight, vitamin A by mouth

Diagnosis	No. of patients	Ester vitamin A			Alcohol vitamin A		
		Range—I.U. vitamin A/100 ml. serum					
		Fasting	Hr. after vitamin A		Fasting	Hr. after vitamin A	
			4	7		4	7
Abdominal pain	1	91	1,113	285	144	2,770	501
Abnormal ureter	1	103	152	266	125	589	255
Asthma	3	68–197	114–418	68–627	4–137	38–638	39–631
Behavior problem	1	80	327	274	27	285	—
Bronchiectasis	1	171	502	361	95	1,700	247
Bronchitis	1	42	114	80	0	148	95
Carotenemia	1	0	220	194	0	205	68
Cirrhosis of the liver	1	315	608	422	437	1,809	977
Dolichocolon	1	121	1,056	448	258	2,364	752
Dysentery	1	42	95	471	114	171	217
Eczema, chronic	1	118	553	787	129	699	407
Gaucher's disease	1	0	34	445	61	277	540
Hypopituitarism	2	80–99	334–2,276	429–1,870	114–148	619–2,812	350–593
Intestinal obstruction	1	163	426	395	186	669	—
Megacolon, congenital	1	19	179	65	80	118	84
Nasopharyngitis	3	0–300	300–1,626	389–1,129	117–285	623–1,994	775–1,068
Neurotic traits	1	72	627	114	87	635	114
Otitis media	1	122	950	597	380	3,602	912
Pneumonia	3	11–148	201–1,376	175–1,129	99–133	167–475	175–483
Rheumatoid arthritis	1	144	300	186	110	285	201
Scarlet fever	1	49	365	300	80	2,003	661
Stenosis of bile ducts	1	11	8	—	—	42	—
Streptococcosis	1	121	714	365	129	1,098	285
Ulcerative colitis	2	57–228	593–3,887	551–2,044	80–190	1,189–3,842	228–6,791

COMPARISON OF THE ABSORPTION OF AQUEOUS AND OILY PREPARATION OF VITAMIN A

The following studies were suggested because of the present widespread interest in the absorption of aqueous preparations of vitamin A. The oily preparations used, which were previously described in this paper, were: Abbott ester vitamin A, which was obtained from the Abbott Laboratories and contained 210,000 I. U. ester vitamin A/gm. of oil; Borden alcohol vitamin A which was obtained from The Borden Vitamin Company and contained 210,000 I. U. alcohol vitamin A/gm. of oil. The aqueous preparations employed were: "Vifort Special, which was prepared by Endo Products, Inc., and contained 60,000 I. U. alcohol vitamin A/gm. dispersed in a 60% aqueous solution of sorbitan monolaurate polyoxy ethylene derivative; Vi-Syneral Vitamin Drops, which was prepared by U. S. Vitamin Corporation and contained 7,000 I. U. alcohol vitamin A/gm. dispersed in an aqueous medium containing sorbitan monolaurate derivative and propylene glycol; "Zymadrops Special," which was prepared by The Upjohn Company

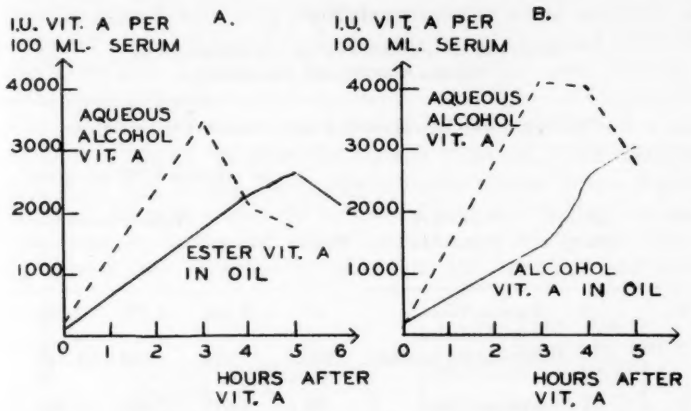

FIG. 4. Vitamin A absorption curves showing the concentration of vitamin A in serum after oral test doses of 14,000 I.U./kg. body weight of vitamin A in the form of oily or aqueous preparations. The curves shown under A represent mean values obtained for three normal children, under B, mean values for four normal children.

and contained 10,500 I. U. ester vitamin A/gm. emulsified in water with the aid of natural gum.

As normal subjects, we used three convalescent boys and four girls who were believed to have no abnormalities in intestinal digestion and absorption. The oral test dose, which was given in capsules, was 14,000 I. U./kg. body weight of vitamin A in order that our results would be comparable with those of other investigators. As is shown in Table V, the absorption of the aqueous "Vifort Special" was compared with the absorption of the oily Borden or oily Abbott product. The first two preparations contained alcohol and the third ester vitamin A. The curves shown in Figure 4 represent the mean

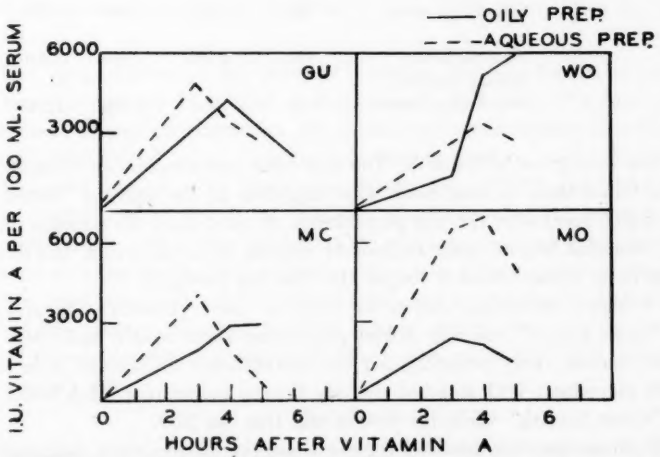

FIG. 5. Comparison of the concentration of vitamin A in serum of four normal children after an oral test dose of 14,000 I.U./kg. body weight of vitamin A in the form of an oily or aqueous preparation.

TABLE V

ABSORPTION OF AQUEOUS AND OILY PREPARATIONS OF VITAMIN A BY NORMAL CHILDREN

Test dose: 14,000 I.U./kg. body weight, vitamin A by mouth

Subject	Age in years	Vitamin A preparation	I.U. vitamin A/100 ml. serum				
			Fasting	Hours after vitamin A			
				3	4	5	6
AN ♀	4	Aqueous Vifort Special (alcohol)	57	3,534	3,226	2,652	—
		Oily-Borden (alcohol)	110	129	319	1,140	—
MC ♀	12	Aqueous Vifort Special (alcohol)	80	3,975	2,056	866	—
		Oily-Borden (alcohol)	152	1,832	2,766	2,835	—
MO ♀	10	Aqueous Vifort Special (alcohol)	91	6,536	6,977	5,081	—
		Oily-Borden (alcohol)	174	2,257	2,086	1,778	—
WO ♂	13	Aqueous Vifort Special (alcohol)	61	2,637	3,447	2,466	—
		Oily-Borden (alcohol)	87	1,338	5,077	5,951	—
AR ♀	5	Aqueous Vifort Special (alcohol)	80	2,288	1,748	1,383	—
		Oily-Abbott (ester)	129	—	1,125	2,120	2,060
BA ♂	12	Aqueous Vifort Special (alcohol)	152	3,363	2,094	1,307	—
		Oily-Abott (ester)	80	—	1,379	2,781	2,288
GU ♂	13	Aqueous Vifort Special (alcohol)	224	4,796	3,359	2,630	—
		Oily-Abbott (ester)	68	—	4,210	2,945	2,151

values of the data given in Table V. The maximum concentration of vitamin A in the serum was found three to four hours after ingestion of the aqueous "Vifort Special" and four to five hours after the oily preparations. In most cases, the aqueous preparation produced somewhat higher concentrations of vitamin A in the serum, but this concentration tended to remain elevated longer after the oily products.

Figure 5 shows individual curves for four of these children. GU absorbed the aqueous "Vifort Special" and oily Abbott preparation about equally well; MC absorbed the "Vifort Special" very promptly, but the concentration of vitamin A in her blood fell rapidly thereafter; WO absorbed the oily Borden preparation much better than the aqueous "Vifort Special," while the reverse was true for MO.

Table VI shows the data obtained for the absorption of the above described aqueous and oily preparations of vitamin A by patients with various diseases. The oral test dose used was 7,000 I. U. vitamin A/kg. body weight. The oily products were dropped into the babies' mouths and given in capsules to the older subjects; the aqueous products

were given by stomach tube or by mouth in capsules or mixed with fruit juice. The concentration of vitamin A was determined in the fasting blood and in the blood four and seven hours after ingestion of the vitamin. Individual curves for four of these patients are given in Figure 6.

From a consideration of Table VI, it is evident that the child CR, with a questionable diagnosis of celiac disease, did absorb the aqueous Vi-Syneral, which contained alcohol vitamin A, better than the oily Abbott ester or Borden alcohol vitamin A products; on the other hand, RI, with a diagnosis of celiac disease, absorbed the aqueous "Vifort Special" and the oily Borden and Abbott products about equally well. Both children, however, showed poor absorption of vitamin A. HU, who had been treated since

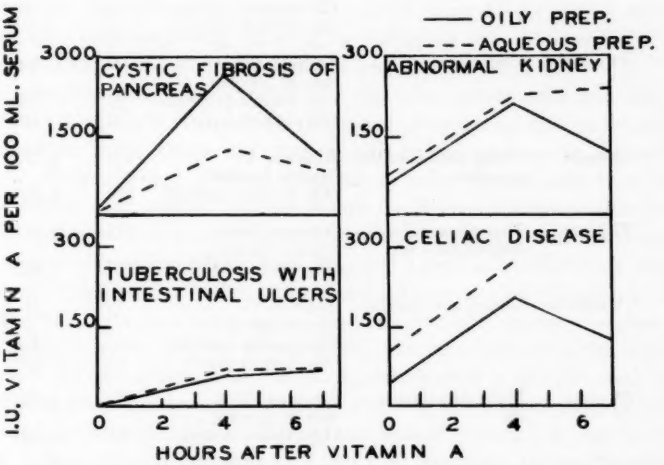

FIG. 6. Comparison of the concentration of vitamin A in serum of four patients after an oral test dose of 7,000 I.U./kg. body weight of vitamin A in the form of an oily or aqueous preparation.

infancy for cystic fibrosis of the pancreas, absorbed the oily Borden alcohol product better than the aqueous Vi-Syneral alcohol product. MA and WO were adults who attained much higher concentrations of vitamin A in the serum after ingestion of aqueous "Vifort Special" than after the oily Borden product, while EC absorbed the oily Abbott ester product much better than "Vifort Special." NI and RH who suffered from decreased ability to absorb fat exhibited poor absorption for aqueous Vi-Syneral and the oily Borden and Abbott products. CA, who later died as a result of tuberculosis associated with many tuberculous intestinal ulcers, was almost unable to absorb "Vifort Special" or the Borden product. CP with diabetes and a questionable diagnosis of cystic fibrosis of the pancreas absorbed the oily Abbott ester product poorly, but both the aqueous "Zymadrops Special," which contained ester vitamin A, and the oily Borden alcohol product well.

DISCUSSION

The data obtained in these various studies justify our drawing certain conclusions. As is shown in Table I, in which the absorption of the oily Abbott ester and the oily Borden alcohol vitamin A products are compared, normal newborn infants do not, in general, absorb vitamin A after oral administration as well as do older children and

TABLE VI

ABSORPTION OF AQUEOUS AND OILY PREPARATIONS OF VITAMIN A BY PATIENTS WITH VARIOUS DISEASES

Test dose: 7,000 I.U./kg. body weight, vitamin A by mouth

Patient	Age	Diagnosis	Vitamin A preparation	I.U. vitamin A/100 ml. serum		
				Fasting	Hours after vitamin A	
					4	7
CR ♂	3 months	? Celiac disease	Aqueous-Vi-Syneral (alcohol)	19	386	167
			Oily-Borden (alcohol)	34	19	38
			Oily-Abbott (ester)	11	72	34
RI ♀	13 months	Celiac disease	Aqueous Vifort Special (alcohol)	99	266	—
			Oily-Borden (alcohol)	87	262	163
			Oily-Abbott (ester)	42	198	122
HU ♂	2½ years	Cystic fibrosis of the pancreas	Aqueous- Vi-Syneral (alcohol)	129	1,227	806
			Oily-Borden (alcohol)	110	2,603	1,208
MA ♀	52 years	Hepatomegaly of undetermined origin	Aqueous-Vifort Special (alcohol)	175	3,561	631
			Oily-Borden (alcohol)	137	1,482	479
NI ♀	9 months	Kidney abnormality	Aqueous-Vi-Syneral (alcohol)	76	217	228
			Oily-Borden (alcohol)	—	201	133
			Oily-Abbott (ester)	61	258	65
EC ♀*	55 years	Multiple avitaminosis	Aqueous Vifort Special (alcohol)	68	2,098	714
			Oily-Abbott (ester)	84	3,690	1,159
WO ♀	22 years	Multiple avitaminosis	Aqueous-Vifort Special (alcohol)	308	2,789	984
			Oily-Borden (alcohol)	331	1,889	1,053
BO ♂	2 months	Otitis media	Aqueous-Vi-Syneral (alcohol)	167	486	—
			Oily-Borden (alcohol)	4	771	—
			Oily-Abbott (ester)	61	357	186
RH ♂	9 months	Steatorrhea	Aqueous-Vi-Syneral (alcohol)	46	350	205
			Oily-Borden (alcohol)	38	236	84
			Oily-Abbott (ester)	23	61	163
CA ♀	40 years	Tuberculosis with intestinal ulcers	Aqueous Vifort-Special (alcohol)	34	65	68
			Oily-Borden (alcohol)	0	61	68
CP ♀	11 years	Diabetes. ? Cystic fibrosis of the pancreas	Aqueous Zymadrops Special (ester)	205	870	410
			Oily-Borden (alcohol)	167	684	597
			Oily-Abbott (ester)	167	182	182
			Oily-Abbott (ester)	125	148	399

* Test dose: 14,000 I.U./kg. body weight vitamin A by mouth.

adults. It is interesting to note that Henley, Dann and Golden[4] found that premature infants did not absorb vitamin A and fats as well as normal full term infants. As is shown in Table I, for the older children, the mean four hour value for the ester series was 1,569 I. U. vitamin A, and for the alcohol series, 817 I. U. This difference seems

significant and does not occur in the case of the newborn infants and adults. However, this difference might disappear in a larger series of children since it is not evident in the curves shown in Figure 4.

In most of our studies with patients, the Abbott ester vitamin A test was performed first because we feel that if a patient absorbs ester vitamin A in oil well, his absorption of fats is normal and it is not necessary to carry out further vitamin A absorption tests unless desired for some special reason. Almost always one or more days were allowed to pass before a second test was done. It was thought that this sequence did not affect the results for the clinical condition of the patients was about the same on both days. Most of the patients were afebrile on these days. There did not seem to be a "priming effect" on the absorption of the various preparations of vitamin A due to the previous dose of the ester. As is shown in Tables IV and VI, many of the fasting Abbott ester values are higher than the fasting values in the following tests. Moreover, no "priming effect" was observed in the studies carried out with normal subjects.

We are now comparing the absorption of the oily Abbott ester and oily Borden alcohol vitamin A products as an additional routine procedure in making the differential diagnosis between celiac disease and cystic fibrosis of the pancreas. In our series there were several children with a previous diagnosis of celiac disease, who were unable to absorb the Abbott ester product, but did absorb the Borden alcohol product very well. This fact, together with other clinical and laboratory findings justified changing their diagnosis to cystic fibrosis of the pancreas. May and Lowe[5] and Gibbs[6] have verified our conclusions that children with this latter disease absorb alcohol vitamin A and ester vitamin A given with Pancreatin well. The observation that the absorbed alcohol vitamin A, even in cases of cystic fibrosis of the pancreas, appears in the blood as the ester indicates that the enzyme that causes the esterification is not pancreatic lipase.

As is evident from a comparison of Tables I and V, the concentration of vitamin A in the serum is often much greater after the test dose of 14,000 I. U./kg. body weight of vitamin A than after the test dose of 7,000 I. U. However, the smaller test dose is better tolerated by patients, especially in the use of the dilute aqueous preparations where relatively large volumes of the solutions must be ingested. The smaller test dose also affords a better opportunity to detect moderately decreased ability to absorb vitamin A and fats.

As Tables V and VI and Figures 4, 5 and 6 indicate, we did not find the striking difference in the absorption of oily and aqueous preparations of vitamin A in favor of the aqueous reported by Kramer, Sobel and Gottfried[1] and Lewis, Bodansky, Birmingham and Cohlan[2] and various other investigators. From conversations and correspondence with these investigators, it is to be concluded that the differences in our results are due largely to the kinds of oily preparations we have employed. Our oily Abbott and Borden products contained 210,000 I. U vitamin A/gm., while they have always used oleum percomorphum containing about 60,000 I. U. vitamin A/gm. Our experience has been that vitamin A in oils of this low potency is rather poorly absorbed and relatively flat vitamin A absorption curves are obtained.

The other investigators have based their conclusions to a considerable degree on the concentration of vitamin A in serum three hours after the ingestion of the test dose. While this is justifiable in the case of the aqueous products, the absorption of the oily products may be only just beginning at this time and the maximum concentration of vitamin A in the serum may not be found until five hours after ingestion of the vitamin.

The fact that the child CP, Table VI, absorbed the oily Abbott ester vitamin A

product poorly, but the oily Borden alcohol product and the "Zymadrops Special," which contained emulsified ester vitamin A, well, is in agreement with the work of May and Lowe.[5] They found that if the emulsified ester vitamin A preparation contained droplets 0.5 to 10 microns in diameter, it was well absorbed by children with steatorrhea, whether due to the absence of lipase or to other causes.

In man, therefore, the absorption of vitamin A may be influenced by many factors, such as: The presence or absence of intestinal enzymes; the presence or absence of bile or bile salts in the intestinal tract; intestinal motility; pathologic changes in the intestinal wall; the form in which the vitamin A is present, whether ester or alcohol; the medium in which the vitamin A is dispersed, whether aqueous or oily; the droplet size of emulsified vitamin A preparations; the concentration of vitamin A, especially in the oily preparations; the composition of the oil in the oily preparations.

Summary

A study was made of the absorption of aqueous and oily preparations of ester and alcohol vitamin A by normal subjects and by patients with various diseases. The oily preparations used were the Abbott product (containing 210,000 I. U. ester vitamin A/gm.) and the Borden product (210,000 I. U. alcohol vitamin A/gm). The aqueous preparations used were: "Vifort Special" (60,000 I. U. alcohol vitamin A/gm.); Vi-Syneral Vitamin Drops (7,000 I. U. alcohol vitamin A/gm.); "Zymadrops Special" (10,500 I. U. ester vitamin A/gm.).

When seven normal children ingested 14,000 I. U. vitamin A/kg. of body weight in the form of aqueous "Vifort Special" or the oily Borden or Abbott products, the maximum concentration of vitamin A in serum was found three to four hours after the ingestion of "Vifort Special" and four to five hours after the oily products. In most cases "Vifort Special" produced somewhat higher concentrations. The vitamin A in the serum tended to remain elevated longer after the oily products. We did not find the striking difference in the absorption of the oily and aqueous preparations of vitamin A in favor of the aqueous reported by other investigators. This seemed to be due to the fact that we used relatively concentrated oily vitamin A products containing 210,000 I. U./gm., while they used oleum percomorphum containing 60,000 I. U./gm.

Four hours after ingestion of 7,000 I. U. vitamin A/kg. body weight in the form of the oily Abbott ester product the mean I. U. vitamin A/100 ml. serum for 35 normal newborn infants, 13 older children and 12 adults was, respectively: 502, 1,569 and 1,300. After ingestion of the oily Borden alcohol product, the corresponding values were, respectively: 688, 817 and 1,273. The absorption of vitamin A by the newborn infants was very variable while the older subjects absorbed both products well.

After oral administration, 13 children with cystic fibrosis of the pancreas absorbed only small amounts of the Abbott ester product but absorbed the Borden alcohol product well, while seven children with celiac disease showed poor absorption of both products. Therefore a comparison of the absorption of concentrated oily preparations of ester and alcohol vitamin A is an aid in the differential diagnosis of these two diseases.

Since patients with cystic fibrosis of the pancreas, anemia, diarrhea, giardiasis, severe malnutrition and some acute conditions absorb alcohol vitamin A in oil much better than the ester in oil, it is suggested that the alcohol form of vitamin A in oil or in an aqueous dispersion or emulsified ester vitamin A would be effective sources of vitamin A in the proper nutrition of these patients.

Patients with celiac disease, intestinal ulcers and certain other diseases absorbed both oily and aqueous products poorly. Other patients showed excellent absorption of the various aqueous and oily products.

Acknowledgments

For the vitamin A preparations used in these studies, we wish to express our thanks to Abbott Laboratories, Endo Products, Inc., The Borden Vitamin Company, The Upjohn Company and U. S. Vitamin Corporation.

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Spanish Abstract

La Absorción de Preparaciones Aceitosas y Acuosas de Ester y Alcohol Vitamina A por Niños Normales y por Niños con Varias Enfermedades

Se comparó la absorción de preparaciones aceitosas de éster y alcohol o vitamina A "predigerida" (210,000/gm. I.U.) en 35 recein nacidos, 13 niños mayores y 12 adultos. A los niños normales se les dió 7,000 I.U./kg. peso de cuerpo de vitamina A oralmente. Los espécimenes de sangre, cuatro y siete horas más tarde revelaron que la concentración máxima ocurrió a las cuatro horas. Después de la ingestión de éster vitamina A, la concentración media en los recien nacidos, niños mayores y adultos fué, respectivamente: 502, 1,569 y 1,300 I.U. vitamina A/100 ml. de suero. Después de la alcohol vitamina A, los valores correspondientes fueron 688, 817, y 1,273 I.U.

Trece niños con fibrosis cística del pancreas, absorbieron alcohol vitamina A mucho mejor que éster, mientras que siete niños con enfermedad celíaca absorbieron ambos malamente; y así ayudaron a hacer la diagnosis diferencial.

Los pacientes con giardiasis, diarrea, anemia y desnutrición severa, absorbieron alcohol vitamina A en aceite mucho mejor que éster.

Se comparó la absorción de preparaciones acuosas y aceitosas de éster y alcohol vitamina A. La dosis de ensayo fué de 14,000 I.U./kg. peso de cuerpo vitamina A. La concentración en suero fué determinada tres, cuatro, cinco y seis horas después de la ingestión. No encontramos marcada diferencia en la absorción de preparaciones aceitosas y acuosas como han encontrado otros investigadores, posiblemente debido a la clase de preparaciones aceitosas que se usaron.

La concentración de suero máxima ocurrió de tres a cuatro horas después de la ingestión de preparaciones acuosas y de cuatro a cinco horas después de preparaciones aceitosas. En la mayor parte de los casos, las preparaciones acuosas produjeron concentraciones un poco más altas. La vitamina A en el suero quedó elevada más tiempo después de las preparaciones aceitosas. Los pacientes con enfermedad celíaca, úlceras intestinales y otras enfermedades absorbieron ambos muy malamente; otros mostraron excelente absorción de ambos.

260 Crittenden Blvd.

GALACTOSE STUDIES IN AN INFANT WITH IDIOPATHIC GALACTOSE INTOLERANCE

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INTRODUCTION

HUMAN infants with a restricted capacity to dispose of ingested galactose may develop hepatic, intestinal, and renal abnormalities as well as malnutrition and cataracts.[1-9] Studies by other investigators on infants with this disorder have been limited to tests based on the oral administration of galactose.[1-9] In only one experiment has the sugar been injected intravenously, and that was at a very small dosage immediately after receiving glucose.[8]

In this paper studies of the disposal of intravenous galactose in an infant with idiopathic galactosemia and galactosuria are reported. In addition the effects of accelerated glucose metabolism on the galactose intolerance of our patient have been determined, in view of previous reports that under these circumstances the utilization of galactose is increased.[10-14] In a second group of tests ethyl alcohol was administered to the patient prior to the galactose, because experiments on healthy adults have revealed that alcohol may also affect the utilization of this sugar.[15,16] Five other infants without evidence of galactose intolerance have served as controls for the experiments with galactose alone.

SUBJECTS

On admission, J.S., the patient with idiopathic intolerance to galactose was an 18-week-old, malnourished, white, male. A history of transient jaundice at the age of four days and frequent bouts of vomiting, diarrhea, and anorexia was obtained.

Examination revealed bilateral nuclear cataracts, hepatomegaly, splenomegaly, and ascites. A normocytic anemia with 2.4 million erythrocytes was present together with glycosuria and albuminuria. The reducing substance in the urine persisted after incubation with yeast for 30 minutes at 37° C. and was identified as galactose by the osazone and mucic acid tests.[17] The serum albumin concentration proved to be 3.65 gm./100 cc. and globulin 2.65 gm. BSP excretion, serum bilirubin, serum lipid fractions, and the responses to glucose and to epinephrine were within normal limits.[18]

Clinical improvement was evident almost immediately after the withdrawal of galactose from the diet and only vestigial cataracts and moderate hepatomegaly were present four months afterward. The patient's growth pattern has been analyzed elsewhere.[19]

The five other infants studied were of approximately the same size as the patient. J.F. and C.Q. were 16 and 18-week-old white males respectively, admitted as feeding problems, but eating well and gaining weight during the week prior to the experiment. R.D., an eight-week-old white male, had been admitted for study as a possible case of

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hydrocephalus, but all findings were within normal limits. D.C. and G.H. were four-week and 28-week-old, Negro male and female infants respectively, afebrile and several days convalescent from upper respiratory infections which had lasted one week.

Experimental Procedure and Methods

All galactose tolerance tests were conducted in the morning after four to five hours of fasting with water as desired. In each study a 50% solution of galactose in water was

TABLE I

Blood Levels and Urine Excretion Following the Intravenous Injection of 1.2 gm./kg. Body Weight of Galactose

	Age (weeks)	Body Weight (kg.)	Time:	Blood: Galactose (mg./100 cc.) 0′	15′	45′	75′	Urine: Volume (ml.)	Excretion of Galactose (gm.)
Convalescent Infants									
1. D.C. Galactose only	8	5.0		6	157	23	13		
2. R.D. Galactose only	8	5.3		0	204	50	12	19.0	0.4
3. J.F. Galactose only	16	3.7		0	212	48	8#	3.5**	0.2
4. C.Q. Galactose only	18	4.4		0	205	64	15	20.0	0.6
5. G.H. Galactose only	28	5.4		0	174	78	15	17.0	0.6
Patient J.S.									
A.									
1. Galactose only	21	5.0		0	222	170	155		
2. Galactose only	24	5.3		2	233	180	157		
3. Galactose only	27	5.5		0	272	208	188		
4. Galactose only	41	8.1		0	239	175	155	30.0*	1.3
B.									
1. Galactose+Insulin	26	5.6		0	194	138	122		
2. Galactose+Glucose (1.0 gm./kg.)	41	8.1		0	197	141	104	38	0.7
3. Galactose+Glucose (2.0 gm./kg.)	26.5	5.8		0	254	164	114		
4. Galactose+Glucose+Insulin‡	28	6.0		0	205	140	99		
5. Galactose†+Glucose+Insulin‡	29.0	5.7		3	88	32	6		
C.									
1. Galactose+Alcohol (0.5 cc./kg.)	29	6.0		2	218	188	168§		
2. Galactose+Alcohol (0.4 cc./kg.)	41	8.1		0	234	202	169	35	1.1

* About 3.0 ml. of urine lost.
** All of urine may not have been collected.
#=82′
† Galactose reduced to 0.5 gm./kg.
‡ Additional glucose necessary at 45 minutes to prevent shocking.
§ At 11 hours this concentration decreased to 0.

injected intravenously during a three minute period. Galactose, 1.2 gm./kg. body weight, was employed in all experiments except one on patient J.S., in which 0.5 gm./kg. body weight of the sugar were injected.

A single galactose tolerance test was performed on each of the convalescent infants, while three groups of studies were carried out on the patient J.S.

Group A: Galactose only was administered. The first experiment of the series was performed when the diagnosis was established, the second three weeks later, and the third and fourth in the sixth and twenty-first weeks of a galactose-free regime.

Group B: The effects of increasing the rate of glucose metabolism on galactose intolerance were determined:

Experiment 1: 2 units of crystallin insulin were administered subcutaneously 15 minutes before the galactose.

Experiments 2 and 3: A 50% solution of glucose in water, 1.0 gm. and 2.0 gm./kg. body weight respectively, was injected intravenously 15 minutes before the galactose.

Experiment 4: Insulin and glucose, in the dosages used separately in Experiments 1 and 3, were given together 15 minutes before the galactose. Additional glucose, 1.0. gm./kg. body weight, was administered orally at the 45 minute point to control the low blood glucose which appeared.

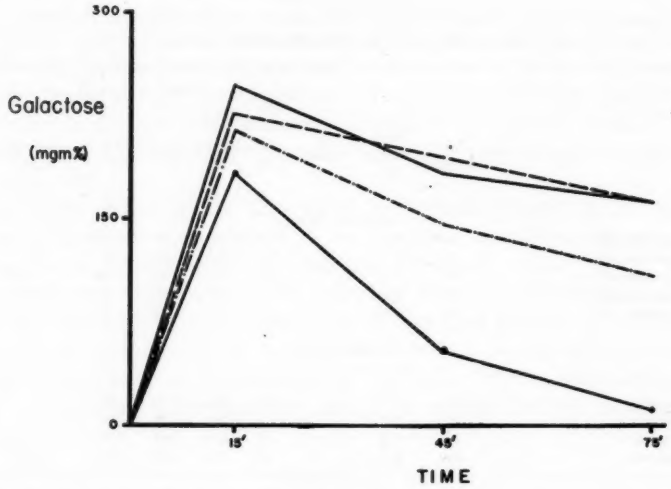

FIG. 1. Blood galactose levels following intravenous injection of the sugar in a dosage of 1.2 gm./kg. body weight.

Lower unbroken line represents average results in five tests on convalescent infants. Upper unbroken line depicts response of patient J.S. in four similar experiments. Broken line indicates levels of galactose attained in two tests on patient J.S. in which alcohol was administered before galactose. Finally, broken-dotted line represents average galactose concentrations in four experiments on patient J.S. during accelerated glucose metabolism.

Experiment 5: Insulin and glucose were given as in Experiment 4, but the dosage of galactose was reduced to 0.5 gm./kg. body weight. Additional glucose was also necessary in this study at the 45 minute point, as in the previous one.

Group C: 3 ml. of 95% ethyl alcohol in 40 ml. of water were administered orally 15 minutes before galactose in the usual dosage. The experiments were conducted six and 19 weeks after the patient had been placed on the galactose-free regime.

Venous blood was collected in bottles containing oxalate immediately before the administration of galactose and again 15, 45, and 75 minutes after the midpoint of the injection. Urines obtained during the 75 minute period of the study were analyzed for galactose. An indwelling catheter was used in the experiment with the female infant, while the males were catheterized prior to and at the end of each test. In the interim voided urine was collected in attached test tubes. Whenever glucose was administered before the galactose, the urine was incubated with 20% bakers' yeast for 45 minutes at 37°C. to remove glucose. 2.0 ml. samples of blood were fermented with the yeast at

room temperature for 30 minutes to remove the glucose. Five washings with distilled water disposed of any reducing substances present in the yeast. The "glucose-free" blood was then analyzed in duplicate for galactose by the iodometric titration method of Somogyi.[20] Recoveries of standard solutions ranged from 97 to 100%. Blood blanks determined in each test (Table I) ranged from 0 to 6 mg./100 cc. and have been taken into account in all calculations.

Results

Experimental results are presented in Table I and Figure 1. The decreased galactose tolerance of patient J.S. was most evident at the 75 minute point when compared to the convalescent infants, even though significant differences were present at 45 minutes. The concentrations at 15 minutes in the studies on patient J.S. (Group A) and on the control group overlap (Table I). This is presumably related to the fact that insufficient time had passed to demonstrate the differences in the rates of utilization of galactose.

The acceleration of glucose metabolism in patient J.S. (Experiments in Group B) by insulin, glucose, or the combination of the two, improved the galactose tolerance of this subject, although it was still well outside the range observed in the convalescent infants. Similar effects were noted when glucose was administered in a dosage of 1.0 or 2.0 gm./kg. body weight, or when a combination of glucose and insulin were employed. Simultaneously, galactosuria was decreased to one-half of that observed in the control study of this subject.

The prior administration of alcohol by mouth (Group C, Experiments 1 and 2) failed to alter the galactose tolerance of patient J.S. as defined in the control studies in Group A. No galactose was presented in the blood stream 11 hours after the injection.

For purposes of clarity these results have been summarized in Figure 1 in the form of the average response under each set of experimental conditions.

Discussion

An infant with inherent inability to dispose of galactose at the usual rate and to a normal degree has provided an opportunity for comparative studies on the disposal of this sugar. The degree of this incapacity has been quantitated by the intravenous administration of galactose with the dosage based upon the body weight. From the data presented in the table and in the figure it is readily apparent that the response of this infant to galactose is clearly separated from that seen in convalescent but otherwise healthy infants. The galactosemia is more pronounced, obviously persists longer, and is associated with a quantitatively much more marked galactosuria. It is to be noted that the tolerance of the convalescent infants for intravenous galactose is at least as good as that observed in adults.[21-23] This is particularly evident when it is recognized that the dosage of galactose in the studies with infants was 1.2 gm./kg. body weight, whereas in the tests in adults only 0.5 to 0.6 gm./kg. was used.[15,16] These findings would suggest that the ability to utilize galactose is not decreased from the normal during convalescence from uncomplicated upper respiratory infections.

Furthermore, it is clear from the experiments presented in Table I, Group A, that the inability of patient J.S. to dispose of galactose at the usual rate persisted despite four months of a galactose-free regime which produced marked clinical improvement. It was possible, however, to demonstrate a reduction in his galactose intolerance following an increase in glucose metabolism. This was observed with both insulin and glucose

given separately and together. This is not a new finding. One of Goldbloom's infants with idiopathic galactosuria, also had a decrease in galactosemia following the injection of insulin.[8] It should be pointed out, however, that these results are at variance with those in three other reported studies on infants with galactosemia. In one study by Mason and Turner, blood galactose concentrations increased following insulin while in the others by Bruck and Rapoport, and by Norman and Fashena, no clear-cut alteration was evident.[4,5,7] It may be that this discrepancy is the result of differences in routes of administration of the galactose, but the possibility that each patient responds in an individual manner can not be eliminated. Certain studies in animals tend to support the existence of a common pattern of response. Thus, healthy adults, dogs, and rats have a significant reduction of galactosuria when glucose is administered intravenously or orally with galactose. [10,11,15,21] Similarly, Wierzuchowski[13] and Pollak and Fehér[14] found that insulin increased the rate of removal of galactose from the blood stream and decreased the urinary excretion of the sugar in dogs following the intravenous injection of galactose.

The site of the improvement in galactose tolerance following the stimulation of glucose metabolism is not evident from these studies. It could occur either in the liver or in peripheral tissues. Although the liver is one of the main organs involved in normal galactose metabolism, extrahepatic tissues are also capable of disposing of galactose in hepatectomized and nephrectomized preparations.[24] The arteriovenous differences in the concentrations of galactose in man demonstrated by Harding and Grant[25] also suggest degradation of galactose in tissues, but the studies are not entirely conclusive. The significance therefore of peripheral utilization of galactose has not been exactly determined. Ordinarily, however, galactose is converted into glycogen in the liver.[21,26,27] It is also known that liver disease is often associated with an abnormal galactose tolerance.[15,22,28,29] It may be significant, therefore, that hepatic abnormalities have been described in subjects with disorders of galactose metabolism.[1-9] Portal cirrhosis was found at the autopsies of the two children who died with similar conditions.[1,3] The infant studied here had jaundice early in life and a strikingly enlarged liver. Supporting evidence of such a relationship is also present in certain animal studies. Thus the livers of the rats studied by Handler[30] were depleted of glycogen and infiltrated with lymphocytes. These facts all point to a relationship between the liver and galactose disposal, but it is not possible to separate clearly cause and effect.

It seems likely that the persistent galactosemia damaged the tissues of the lens and the liver in this patient, in view of the clinical improvement following galactose withdrawal despite the unaltered galactose tolerance. The finding that glucose improved the galactose tolerance of patient J.S. points not only to an interrelationship of the metabolism of these two substances, but has also certain therapeutic implications. It would appear logical to conclude that infants with galactose intolerance should receive a high carbohydrate intake in addition to restriction of galactose. This would minimize the effects of any galactose which might be included inadvertantly in such a patient's diet. The single experiment on the patient J.S. in which 0.5 gm./kg. body weight of galactose was disposed of within 75 minutes following the administration of glucose further supports this view.

It is to be noted that the combination of alcohol and galactose did not further impair the galactose tolerance of the patient. This differs from the effect of alcohol upon galactose metabolism in healthy adults where small amounts of alcohol cause a temporary

intolerance to galactose, presumably by interference with the conversion of galactose into glycogen in the liver.[16] The lack of effect of alcohol in the patient would suggest that the site of the defect in idiopathic galactose intolerance and the site of action of alcohol in normal subjects who develop transient inefficiency of galactose utilization may be the same.

Conclusions

Galactose metabolism has been studied in a group of convalescent children and in one patient with galactosuria, hepatomegaly and splenomegaly, and cataracts. The galactose tolerance of the convalescent infants studied following intravenous injection of the sugar was similar to that observed in healthy adults. Galactose intolerance as measured by test doses of the sugar, persisted in the infant with galactose intolerance despite clinical improvement on a galactose-free diet. Simultaneous administration of glucose or insulin with the galactose accelerated the rate of disposal of the latter partially, but not completely, toward normal. Alcohol did not alter the galactose tolerance of the patient.

Acknowledgment

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SPANISH ABSTRACT

Estudios Galactosos en un Infante con Intolerencia Galactosa Idiopática

El metabolismo galactoso ha sido estudiado en cinco infantes convalescientes y en un paciente con galactosuria idiopática, hepato- y esplenomegalia, y cataratas. Concentraciones de sangre venosa de galactosa y grado de galactosuria fueron determinadas a intervalos después de inyecciones intravenosos rápidas de una solucion de 50% de azúcar en agua, en dosis de 1.2 gm./kg. peso de cuerpo. La tolerancia galactosa de los infantes convalescientes fué similar a la de los adultos sanos. El paciente, sin embargo, a pesar del mejoramiento clínico a dieta libre de galactosa, tenía intolerancia persistente al azúcar con niveles de sangre de 75 minutos entre 164 mg./100 cc. en contraste con 13 mg./100 cc. en los infantes convalescientes. La administración simultánea de glucosa, 1.0 a 2.0 gm./kg. peso de cuerpo, o insulina, 2.0 unidades subcutaneamente, con la galactosa aceleró la velocidad de disposición de la última parcialmente; pero no por completo, hacia el estado normal. La galactosemia a 75 minutos fué 42 a 65 mg./100 cc. menos que en los estudios de control en el paciente, y la galactosuria fué reducida concomitantemente. El alcohol no alteró la tolerancia galactosa del paciente. Esto sugiere que, además de la restricción galactosa, los pacientes con intolerancia al azúcar reciben una toma alta de hidrato de carbono para reducir al mínimo los efectos de cualquier galactosa que haya sido inadvertidamente incluída en la dieta.

125 De Soto St.

MULTIPLE CYSTIC TUBERCULOSIS OF BONE

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MULTIPLE cystic tuberculosis of bone is a type of osseous tuberculosis which affects usually the diaphysis of long or short-long bones and less frequently flat bones, which presents a cystic appearance on X-ray examination, is relatively painless, prone to break through the overlying tissues, and of itself bears a good prognosis. Whether or not it is identical to or akin to the condition described by Jungling[1,2] as osteitis tuberculosa multiplex cystica is debatable, but it does represent a specific type of osseous tuberculosis.

It is a somewhat uncommon disease. Although reported frequently in the foreign literature, it has received relatively little recognition in American pediatric publications[3-8] and is unfamiliar to many.

The following case is illustrative of the condition. The history and course are similar in several respects to those of many patients hitherto reported.

CASE REPORT

H.V., an 11½-year-old white male, was referred to the Boston Floating Hospital from the Children's Clinic of the Boston Dispensary because of swelling below the left knee of one month's duration.

At the time of admission, the patient's mother was in a sanatorium because of pulmonary tuberculosis. The child's health had been good. A tuberculin test four months before entry was said to have been negative.

The child was first seen at the Children's Clinic in July 1946 because of a small soft swelling over the right scapula. This had first been noted in May 1946, and had disappeared slowly only to reappear the following month. During the next two weeks it increased in size, becoming red and painful. On examination there was a tender, fluctuant mass 5 x 6 cm. located just above the spine of the right scapula. This was incised and about 15 cc. of thick yellow pus and cheesy material were evacuated from what appeared to be a cystic structure. At the time of this visit a soft swelling below the left knee was also noted. The patient stated that he had been injured there eight months previously, and that for 24 hours following the injury there had been swelling and pain. Thereafter there were no symptoms until one month prior to entry when swelling again followed trauma.

There was moderate tenderness but no pain and no limitation of motion. X-ray examination of the knee at this time revealed a destructive lesion of the anterior surface of the proximal portion of the left tibia with soft tissue swelling surrounding it. It was thought that the process was most likely malignant. A chest X-ray was negative.

On admission the child was seen to be well developed and well nourished. The temperature was normal. The face was rather pale. There were no abnormalities of the head and neck. The thoracic cage was remarkable only in that there was a slight protrusion of the sternum. The lungs were resonant to percussion, breath sounds were vesicular throughout and no rales were heard. The heart, abdomen and reflex responses were normal. A wound with drain was noted over the right scapula. Over the proximal anterior aspect of the left tibia there was a soft swelling measuring about 4 cm. in diameter. The circumference of the leg at this point measured 28.5 cm., while at a corresponding level of the right leg the circumference was 27 cm. There was no limitation of motion at the joint. The distance from the anterior superior iliac spine to the internal malleolus measured 122 cm. on the left, 124 cm. on the right. No other abnormalities of the extremities were noted.

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Laboratory data: Erythrocytes numbered 3.1 million/cmm., Hgb. 10.4 gm., leukocytes 8,300/cmm. with 1% eosinophils; 69% polynuclear leukocytes, 29% lymphocytes and 3% monocytes. The urine contained albumin 10 mg./100 cc. on admission but was negative thereafter. The blood NPN was 29 mg./100 cc., calcium 8.9 and 11 mg., inorganic phosphorus 3.8 and 3.5 mg., alkaline phosphatase 3.0 and 3.1 Bodansky units, total protein 7.8 gm., cholesterol 242 mg. of which 181 mg. was esterified. The sedimentation rate was 31.5 mm. in one hour (Wintrobe). The Hinton test was negative. A tuberculin test, using 0.0005 mg. (1:20,000) of tuberculin, was positive.

FIG. 1. X-ray showing cyst-like changes in the proximal part of the right femur.

During his first two weeks in the hospital the child's temperature ranged between 37.6°C. and 38.3°C. daily, thereafter between 37.3°C. and 37.6°C. On the sixth day the mass over the left tibial tubercle was incised. The subcutaneous tissue was found to be thickened and granulation tissue was noted. On further exploration it was found that the lesion extended down into a bony cavity measuring 2 x 3 cm. The granulation tissue was removed until normal bone was reached.

Further X-ray studies revealed that the skull, hands, feet and lungs were normal. The right femur was found to be affected by a large multicystic lesion about 14 cm. in length extending downward from the lesser trochanter. Some of the cystic areas extended from the medulla to the

very edge of the cortex and one on the lateral surface penetrated the cortex and elevated the periosteum. The cortex was prominently thickened and the area presented an appearance similar to that in the left knee. (Fig. 1.) The acromium of the scapula was involved in a destructive lesion with the same cystic appearance. An intravenous pyelogram was normal.

On the 12th hospital day the operative wound over the left tibia broke down and greenish purulent material drained therefrom, similar to that which was constantly draining from the wound over the scapula. At this time several small darkly pigmented spots* were noted on the anterior chest, the lumbar region and the right thigh.

A biopsy of the lesion of the right femur revealed that the bone was considerably enlarged in this area. The periosteum was not adherent to the bone at the lower end of the incision and an extensive abscess was found; this was filled with caseous material and yellow pus and led into the medullary canal. The postoperative diagnosis was tuberculous abscess of bone. Direct smear of the material obtained revealed the presence of acid-fast bacilli. Later the pathologic report of the material from this area and from the tibia was tuberculous osteomyelitis. Inoculation of the material into guinea pigs was followed by the development of typical tuberculous lesions.

The three operative wounds continued to drain greenish purulent material during the rest of the hospital stay. After six weeks in the hospital the patient was transferred to the Lakeville State Sanatorium. We are indebted to Dr. Leon Alley, Superintendent, for information on the subsequent course. The sinuses over the tibia and femur healed but there was still some drainage from that over the scapula. X-rays of the bones bore out the clinical signs of improvement, there being evidence of subsidence of the active process and signs of repair. X-ray examination of the chest showed enlarged tracheobronchial nodes, a finding which was not present while he was in this hospital.

Summary

Cystic tuberculosis of bone is an uncommon but by no means rare disease. It is often confused with syphilis, pyogenic osteomyelitis, malignant tumor, polyostotic fibrous dysplasia, eosinophile granuloma and other disorders which affect the skeleton. The diagnosis depends, first, on familiarity with the condition; second on the histologic features of material removed by biopsy; and, finally, on the demonstration of tubercle bacilli by guinea pig inoculation or by culture in the purulent discharge or in the excised tissues of the sinus.

A report of an exemplary case is presented.

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* The patient was seen by Dr. S. J. Thannhauser, who expressed the opinion that the pigmentation was of no consequence and that the general picture was consistent with a diagnosis of tuberculosis of bone and was not due to xanthomatosis, von Recklinghausen's disease or polyostotic fibrous dysplasia.

SPANISH ABSTRACT

Tuberculosis Cística Múltiple de los Huesos

Este caso ilustra las características típicas de la tuberculosis cística múltiple de los huesos. El exámen mostró una herida en derrame sobre la escápula derecha y una hinchazón suave sobre el aspecto anterior proximal del tibia izquierdo. El ensayo tuberculino intradérmico en una dilución de 1:20,000 fué positivo. Todos los ensayos de laboratorio resultaron esencialmente normales.

Los estudios rayos X revelaron una lesión destructiva de la superficie anterior de la parte proximal del tibia izquierdo. El fémur derecho presentó una lesión multicística grande que se extendía hacia abajo del trocánter menor. El proceso acromio de la escápula derecha también estaba complicada con una lesión destructiva con la misma apariencia cística, y la radiografía del pecho fué negativa.

Las incisiones de la hinchazón sobre el tibia izquierdo y de la lesión del fémur derecho continuaron derramando una materia verdosa purulenta. La inoculación de este derrame en un cobayo resultó positiva para tuberculosis. El frotis directo reveló baccilos firmes a ácidos. El exámen patológico de la materia fué interpretado como ósteomielitis tuberculosa. El pronóstico es bueno.

20 Ash St.

AN OUTBREAK OF NAUSEA, VOMITING AND DIARRHEA ON A MATERNITY SERVICE; TRANSMITTED TO A CHILD CARING INSTITUTION AND TO PRIVATE HOMES

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New York, N.Y., and Kew Gardens, L.I.

THE diarrheal diseases of newborn infants were grouped indiscriminately until recently. However, some order of classification is gradually emerging from this confusion and outbreaks can now be differentiated such as true epidemic diarrhea of the newborn,[1-3] salmonella infection of the newborn,[4,5] and diarrhea accompanying parenteral infections such as pneumonia and sepsis. The pattern of these outbreaks exhibit certain distinctive clinical and epidemiologic features that render them subject to recognition and control. Nevertheless, there still remain cases of diarrhea of the newborn that require further study and classification.

Much attention has been focused on the syndrome, "Epidemic Nausea, Vomiting and Diarrhea," a first description of which appeared in the literature in 1921.[6] Many reports have indicated the widespread nature of the disease. According to Reimann and his co-workers,[7-9] it is endemic, sporadic and at times an epidemic disease or group of diseases which differs from the recognizable forms of bacillary dysentery and the acute food poisonings. It is clinically mild, and sporadic cases may occur in a community for some time before large outbreaks take place. The disorder may occur at any age, although school children and young adults show greater susceptibility. While outbreaks may occur during all seasons, they are especially prevalent in the fall.

Reimann and his collaborators have estimated that the incubation period averages two days with the extremes between 30 hours and seven days. In order of frequency, the following symptoms occur: anorexia, nausea, vomiting, diarrhea, dizziness, generalized aches, and abdominal discomfort or cramps. Less often chilliness and fever may appear, and occasionally signs of involvement of the upper respiratory passages, bradycardia and constipation. Recovery in the majority of instances takes place in from 24 to 48 hours. The reports on this form of diarrheal disorder have dealt mostly with older children and adults.

Brown, Crawford and Stent[10] have, however, described its occurrence among newborn infants on the maternity service of a general hospital. The infection was later noted among the mothers and maternity service personnel, with subsequent spread to other wards of the hospital and to the general nursing personnel. The adults had diarrhea, abdominal cramps, nausea, vomiting and low grade fever. The babies exhibited a diarrhea of greenish watery stools with mucus but no blood. Occasionally there was vomiting. None of the babies showed pyrexia. Weight losses averaged about 500 gm. The clinical course in the babies was mild with recovery in about four days. Fecal cultures were persistently negative. The mildness of the outbreak among the newborn infants with concurrent infection among the mothers and the hospital staff suggested that the disorder

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differed from a previously observed epidemic of virulent and highly fatal diarrhea of the newborn.

More recently, Cook and Marmion[11] described another outbreak of this type of gastroenteritis in a maternity hospital. According to these investigators the clinical course in the newborn babies was difficult to assess because of the mildness of symptoms. They were also of the opinion that the outbreak was quite different from true epidemic diarrhea of the newborn with its severe diarrhea, toxicity and high fatality rate, and

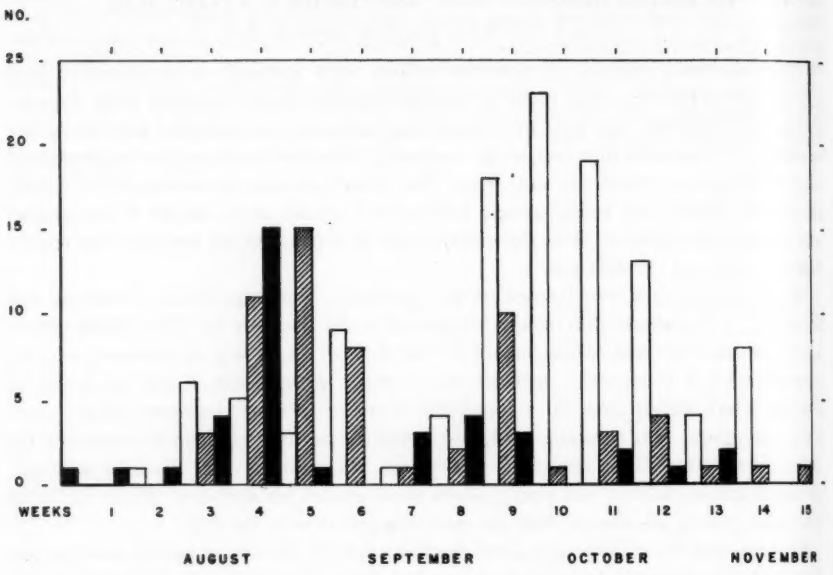

FIG. 1. Sequence of appearance of cases among mothers, babies and nurses on maternity service. Key: Black—mothers; White—babies; Lined—nurses.

also from the combination of herpetic stomatitis and diarrhea in infants reported by Buddingh and Dodd.[12,13]

THE OUTBREAKS

An outbreak of this syndrome took place on the maternity services of a large general hospital in New York City. The source case was a mother in an obstetric ward. The infection spread rapidly to other mothers in the ward and to the babies in the nurseries, and then to the maternity service personnel. The infection was subsequently transmitted to inmates of a child caring institution, and to the residents of a tenement house in the community.

PRIMARY OUTBREAK IN MATERNITY HOSPITAL

Source Case: On August 3, 1946, a mother was admitted to the maternity service of a general hospital. Four days after delivery the mother developed abdominal cramps and diarrhea, but no fever nor vomiting. The source of her illness was not known. It was not considered serious and she was not isolated. Her baby was well. Following this initial case, 32 additional mothers became similarly affected during the next 3½ months. (Figure 1). About 600 mothers were exposed with an attack rate of 5.5%.

Spread of Infection into the Nurseries: The first baby became ill with diarrhea one week after the appearance of the first case. A second baby became ill nine days later. Subsequent cases then appeared in rapid succession until 114 infants, among 586 exposed, became infected by November 15, 1946. The attack rate was 19.4%

Spread of Infection to the Maternity Service Nurses: One week after the first case appeared among the newborn infants, instances of nausea, vomiting and diarrhea occurred among the nurses on duty in the maternity wards and in the nurseries. By that time three mothers and two babies had become ill (Figure 1). Illness then appeared among nurses on duty in other parts of the hospital. In all, 50 nurses became ill. Of these nurses 20 were in the maternity wards and in the newborn nurseries, 18 were on duty in the pediatric wards to which the sick infants were transferred, and 12 worked in other parts of the hospital. Contact of these latter nurses with the maternity service staff may perhaps have occurred in the nurses' dormitory.

Transmission of Infection to Infants' Home

The home affected is a modern institution giving temporary shelter to infants and children from two weeks to six years of age. They are cared for in groups in six dormitory type nurseries with capacities of 12 cribs each. Each of the groups is separated in age by progressive steps of about six months or more. Infants and toddlers in nurseries 1, 2 and 3 are fed in their wards. The older children in nurseries 4, 5 and 6 eat in a common dining room on another floor of the building. Formulas are prepared in a special milk laboratory.

The outbreak which lasted 57 days, began about October 6, 1946 among the small infants in nursery 1 and spread to nursery 3 on October 17. Fifty-eight infants and children were exposed and 28 became ill with diarrhea and associated symptoms; an attack rate of 48.3% (Table I). Four nurses and one teacher among a group of 19 also developed diarrhea. Surprisingly enough, no illness appeared among 21 additional adults comprising the administrative and clerical staffs and the food handlers not in direct contact with the babies.

Source Case: On October 2, 1946, an exposed 10-day-old infant was transferred from the contaminated nursery of the maternity hospital experiencing the original outbreak to nursery 1 of the infants' home.

The baby, M.B., male, white, was born normally on September 23, 1946. During its stay at the maternity hospital the infant appeared well. On the fifth day the mother experienced an attack of diarrhea along with several other maternity patients. The baby was transferred to the infants' home on October 3. Physical examination showed a normal baby whose buttocks were excoriated. Three days after admission, diarrhea developed and became worse during the next five days. Anorexia and fever were not present and vomiting did not occur. With the appearance of mild dehydration on the fourth day of illness the baby was transferred to a hospital for treatment. Recovery was uneventful and the baby was returned to the infants' home on November 4. He remained well until November 26 when diarrhea recurred 51 days after onset of initial involvement. The second attack was mild with no constitutional symptoms and lasted only three days.

Spread of Infection to Other Infants and to Older Children: On October 14, 1946, eight days after onset of the first case in nursery 1, a second baby became ill. The diarrhea in this case was mild without fever or vomiting and lasted only two days. The outbreak then spread to the infants and children in all nurseries (Table I).

Spread of Infection to Nurses and Teachers: On November 6, two nurses and a

TABLE I

SPREAD OF INFECTION AMONG BABIES IN THE VARIOUS NURSERIES OF THE INFANTS HOME

Nursery Number	Age (Months)	Onset of Diarrhea	Infants and Children Exposed	Number of Cases
1	0–6	Oct. 6	12	11
2	6–12	Oct. 19	11	2
3	12–18	Oct. 17	8	6
4	18–24	Oct. 20	8	6
5	24–36	Oct. 25	7	2
6	36–72	Nov. 8	11	1
Infirmary	—	—	1	0
Total			58	28

teacher became ill with diarrhea. Two of these individuals also experienced nausea and vomiting. One of the nurses attended the babies in nursery 1 and also prepared the infants' formulas. The second nurse was assigned to duty in nursery 3 and the teacher in nursery 5. On November 7, a third nurse who worked in nursery 5 developed loose stools but no other symptoms. The last nurse took ill on November 12.

TRANSMISSION OF INFECTION TO FAMILIES IN TENEMENT HOUSE

The marked communicability of the cases in the primary outbreak is further illustrated by the probable introduction of the infection to occupants of a tenement building.

Source Case: Mrs. R. Z., age 32 years, white, was admitted in labor on August 29, 1946 to the hospital experiencing the original outbreak. Delivery was uneventful. On August 31, diarrhea occurred which continued to September 2, when the mother signed out of the hospital against advice. Her baby did not show signs of illness.

The mother lived in an eight-family multiple dwelling. Following her return home, 14 persons in four apartments of the building became ill with nausea, vomiting and diarrhea between September 4 and 11. There were 34 occupants in the building and 20 lived in the four apartments in which the cases of gastro-enteritis occurred. The apartment in which Mrs. Z. lived was overcrowded with 10 other occupants, seven of whom became acutely ill with nausea, vomiting and diarrhea (Table II).

CLINICAL PICTURE

The Newborn Infants: Among the newborn babies in the nurseries, diarrhea was the presenting symptom. The onset was insidious. In fact the milder cases could have been overlooked easily had there not been knowledge of existence of the outbreak. Vomiting was infrequent. The diarrhea varied from occasional pale brown or greenish semi-liquid or watery stool with no blood or mucus to a diarrhea of moderate severity. Dehydration was minimal or absent. Other constitutional signs or symptoms were lacking. Weight losses were not significant. Among the 114 sick newborn babies only 11 had febrile reactions ranging between 37.7° and 40.0°C. The duration of illness was from two to four days and no complications or deaths occurred. The infants responded readily to ordinary therapeutic measures. The mild clinical picture bore no similarity to the severe symptoms of true epidemic diarrhea of the newborn.

The Older Infants and Children: In this age group the illness resembled more nearly that in the adult. The full syndrome was well established within a few hours after onset. Recurrent attacks were seen in seven babies at the infants' home. The intervals between first and second attacks were as follows: 7, 8, 9, 15 (2 cases), 18 and 51 days. One of these cases, a 17-month-old male infant whose first recurrence took place 15 days after an initial attack, had a third bout of illness 21 days after the second. Another baby, female of 26 months, had a second episode of illness nine days after the first, a third attack 25 days later, and a fourth bout seven days after cessation of the third period of sickness.

The Adults: In the adults the onset of infection was striking in its suddenness. Illness began abruptly with nausea, often followed within a few hours by vomiting. Occasionally, abdominal discomfort or generalized abdominal cramps were the first complaints. Frequently, the time of appearance of the pains could be set with accuracy. Watery diarrhea

TABLE II

SPREAD OF INFECTION AMONG THE OCCUPANTS OF APARTMENTS IN TENEMENT HOUSE

Number	Name	Age (Years)	Apartment Number	Onset of Illiness
1	R. Z. (Source Case)	32	7	Aug. 31 (returned to apt. Sept. 2)
2	H. K.	63	4	Sept. 4
3	F. B.	3	3	Sept. 5
4	E. Z.	13	7	Sept. 6
5	D. Z.	9	7	Sept. 6
6	J. Z.	4	7	Sept. 6
7	T. Z.	6	7	Sept. 6
8	J. Z.	37	7	Sept. 8
9	J. K.	32	4	Sept. 9
10	N. K.	20	4	Sept. 9
11	N. W.	29	6	Sept. 9
12	W. Z.	8	7	Sept. 10
13	C. Z.	6	7	Sept. 10
14	M. B.	7	3	Sept. 11
15	A. B.	26	3	Sept. 11

appeared after a lapse of several hours and was mild in comparison with the degree of nausea and vomiting. No blood was in the stools. In some adults the diarrhea was moderately severe and protracted, while in others it did not occur at all. Febrile responses were absent in the majority. The highest level was 38.3°C. Lassitude or weakness was occasionally seen following the subsidence of the acute illness, but recovery was in most instances prompt. Lacking were symptoms referable to the respiratory tract or the nervous system, such as coryza, sore throat, headache and vertigo. The duration of illness in the adults was one to two days. One of the student nurses at the maternity hospital experienced a recurrent attack after 10 days between first and second episodes.

Incubation Period: During the outbreaks at the maternity hospital and the infants' home, an attempt was made to determine the incubation period of the disease in the babies. Figure 2 shows the day of first appearance of diarrhea in 88 newborn babies who were placed in the contaminated nursery after onset of the outbreak. Seventy-seven (87.5%) became ill within the first six days after exposure, the larger number (30 babies

or 34%) coming down on the third day. The median incubation period was between two and three days with a range from one day to 21 days.

At the infants' home, nine babies ranging in age from 14 days to 24 months were admitted to the institution during the outbreak. The interval between the date of admission of these babies and the onset of diarrhea is also indicated in Figure 2.

Bacteriology: Bacteriologic studies of the stools of the infants, mothers and nurses at the maternity hospital, of the infants and adults at the infants' home and of the occupants of the tenement house failed to show enteric bacterial pathogens. No virus studies were made. Cultures of the infant feeding formulas and rubber nipples gave no

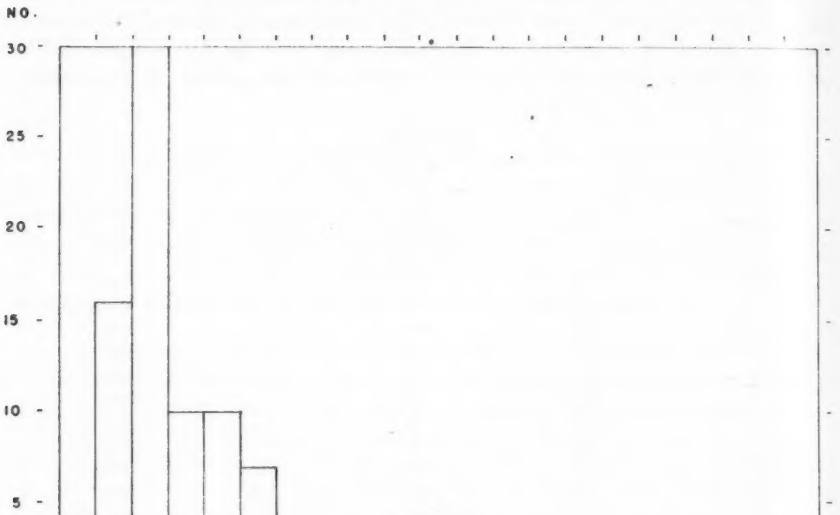

FIG. 2. Time (Days) of onset of diarrhea in 88 newborn babies (white columns) who were placed in contaminated nursery after onset of outbreak and in 12 older infants and children (lined column) who were admitted to the infants' home after occurrence of the initial case.

significant findings. Investigation of the water and food supplies at the hospital also showed no suggestive results.

The disease has not been reproduced in animals. Unsuccessful results have attended inoculation of chorioallantoic chick embryos. Experiments on human volunteers have brought about the disease by the inhalation of a fine mist of filtered nasopharyngeal washings or of the stools of patients, or by the oral administration of stool suspension and throat washings. The feeding of embryonated chick egg blind passage material has failed to cause the disorder.[7-9,14,15]

Differential Diagnosis

A clear-cut concept of the various diarrheal disorders to which newborn infants are peculiarly susceptible is essential in the diagnosis, treatment and prevention of these disorders. Careful clinical and epidemiologic studies of diarrheal outbreaks in newborn infants will in many instances serve to distinguish the various disease entities. Epidemic nausea, vomiting, and diarrhea in newborn infants as described in this report and in England by Brown, Crawford and Stent[10] and by Cook and Marmion,[11] may be differentiated from other primary diarrheal disorders, such as epidemic diarrhea of the newborn and infection with salmonella organisms.

It is unfortunate that considerable confusion has arisen in terminology. For example, the diagnosis of epidemic diarrhea of the newborn should by definition[1-3] be restricted to a specific disease entity affecting newborn infants only. Laxity in usage has resulted in its application to undifferentiated diarrheal disorders and even to salmonella infections occurring not only during the neonatal period but also during the first year of life.[16-19] We agree with Watt[20] that the term epidemic diarrhea of the newborn has erroneously been made a diagnostic scrap basket and that specific causation has been ignored. A similar confusion has characterized attempts to assign the causative role in epidemic diarrhea of the newborn to filterable viral agents that have been isolated experimentally in other forms of diarrhea.[12,13,16,21]

A large group of diarrheal diseases of the newborn has not as yet lent itself to breakdown and to accurate classification. Cummings[22] believes that many of these unclassified outbreaks are due to massive bacterial contamination with organisms of low or no pathogenicity in the presence of deficient nursery care. The paracolon bacilli may possibly be mentioned in this connection.[23]

Summary

An outbreak of epidemic nausea, vomiting and diarrhea in newborn infants is described. The communicability of the disorder is demonstrated by its direct spread to the residents of a child caring institution and to the occupants of a nearby tenement house. We are in agreement with the observations of Brown, Crawford and Stent[10] and those of Cook and Marmion[11] that the condition is a relatively mild one in newborn infants and that it should not be confused either clinically or epidemiologically with the syndrome epidemic diarrhea of the newborn.

A differential diagnosis should be made between this disorder and epidemic diarrhea of the newborn, salmonella infection of the newborn, and the diarrhea accompanying stomatitis in young infants, and should be based on clinical and epidemiologic factors.

Outbreaks in nurseries for newborn infants should be studied carefully and indiscriminate grouping of cases avoided. Distinctive and constant clinical and epidemiologic features should be sought in each outbreak to separate it from the general group of diarrheal disorders of the newborn.

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SPANISH ABSTRACT

Un principio de Naúsea, Vómitos, y Diarrea en un Servicio de Maternidad: Transmitido a una Institución al Cuidado de Niños y a Casas Particulares

Se describe un principio de una naúsea epidémica, vómitos y diarrea en infantes recien nacidos. La comunicabilidad del desorden queda demonstrada por su propagación directa a los residentes de una institución al cuidado de niños y a los ocupantes de una casa de vecindad. Estamos de acuerdo con las observaciones de Brown, Crawford y Stent[5] y con las de Cook y Marmion[6] que la condición es relativamente suave en los infantes recien nacidos y que no se debe de confundir ni clinica ni epidemiologicamente con la diarrea epidémica síndrome de los recien nacidos.

Debe hacerse una diagnosis diferencial entre este desorden y la diarrea epidémica de los recien nacidos, la infección salmonella del recien nacido, y la diarrea que acompaña la estomatitis en los infantes, y debe de basarse en factores clínicos y epidemiológicos.

Deben estudiarse detenidamente los principios en casas de niños y evitar el agrupamiento indistintivo de casos. Las carcaterísticas clínicas y epidemiológicas distintivas y constantes deben de buscarse en cada principio para separarlo del grupo general de desordenes de diarrea del recien nacido.

145 E. 61st. St.

CONGENITAL ANKYLOGLOSSIA (TONGUE-TIE) ASSOCIATED WITH GLOSSOPTOSIS (RETRUDED MANDIBLE) AND PALATUM FISSUM (CLEFT PALATE)

By HANS MAY, M.D., AND LIN T. CHUN, M.D.
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THIS case is presented because of the unusual degree of tongue-tie found in an infant with retruded mandible, glossoptosis, and cleft palate. Similar cases and their complications have been discussed in previous literature but in none has there been described an associated ankyloglossia.

The complications which might arise are mechanical obstruction of the airway to cause respiratory embarrassment with retraction of the sternum and cyanosis, difficulty in swallowing with subsequent malnutrition, and eventual death.

CASE REPORT

J.M., a five-day-old white male infant was admitted to the Mary J. Drexel Children's Hospital with difficulty in breathing and swallowing. The infant had been delivered by cesarian section because of toxemia of pregnancy in the mother. The birth weight was 2.9 kg.

At birth, it was noted that the mandible was short which gave the infant an "Andy Gump" profile. When the neck was flexed forward, difficulty in breathing became apparent and this was relieved by extending the neck and also by pulling the tongue forward.

There was a marked tongue-tie and the tongue appeared to be jammed back into the pharynx. A complete cleft of the soft palate was also present. Neurologic examination was essentially negative and no paralysis of the tongue was noted. X-ray of the mandible showed normal articulations and it was thought to be of normal size and development.

From the beginning, there was difficulty in feeding as the tongue seemed to impinge against the pharynx posteriorly. Liquids given by mouth spilled out from the sides and he was unable to hold a nipple between his tongue and palate. Gavage feedings had to be used entirely.

It was noted that when the tongue fell back into the pharynx, the infant became dyspneic and cyanotic. To remedy this condition, forward traction was placed on the tongue, by passing two sutures through it and attaching them to two rubber bands which were anchored to the anterior chest wall by adhesive tape. This was done on the sixth day of life. Relief in breathing followed this procedure, but in two days, the sutures cut through the tongue. Obstructive breathing with cyanosis occurred again on the ninth day of life. A tracheotomy was done under local anesthesia which gave immediate relief.

On the 28th day of life, the following operation was performed: Using general anesthesia it was possible to investigate the various oral deformities further. There was a cleft through the soft palate. The bony palate was intact. It appeared that the child had only a slight degree of retrusion of the mandible. The most conspicuous deformity was the tongue, which was tied down to the floor of the mouth. The front part of the tongue, which was thought to be the tip was in reality the body. The tip was bent acutely downward and backward so that it was not visible.

With a V-shaped incision the mucous membrane of the floor of the mouth was incised on either side of the buried part of the tongue. The lateral wound edges were reflected. It was possible to free the tip of the tongue which was grasped with a traction suture and pulled forward. Under sharp dissection, the tongue could be developed almost to full length. The raw surface beneath the tongue was closed by suturing the lateral mucosal edges together. The tongue still had a tendency to fall back into the cleft of the palate, hence, the cleft was closed with the Axhausen technic.

From the Children's Hospital of the Mary J. Drexel Home, Philadelphia, Pa.
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Following this operation, the tongue moved more freely but was not entirely corrected as it could not be brought out to its full length. The sutures of the posterior third of the cleft palate tore loose so that only the anterior two-thirds of the cleft was closed. The child appeared to breathe better even when the tracheotomy tube was deliberately closed, but was still unable to take feedings by mouth which necessitated further gavage feedings. The tracheotomy tube was removed after a month. Following this, he had only occasional attacks of difficulty in breathing but no attacks of cyanosis.

At the age of 63 days, another attempt was made to correct the tongue-tie: The tongue, which had been developed to full length in the first operation, had again retracted to some degree. It was held in front by scar tissue, where under normal conditions the frenulum would be situated. The scar tissue was incised in such a way as to form a "Z." After the two triangular flaps had been developed they were interchanged; in other words, a typical Z plasty was performed, which allowed the tongue to be brought out to its full length.

The day following the last operation, the infant had a sudden attack of obstructive breathing with marked retraction of the chest wall and sternum. Bronchoscopy was performed and moderate injection of the larynx and trachea was found, but no foreign body could be seen. Because of the continued difficulty in breathing, a second tracheotomy was done through the same site. There was immediate relief following this procedure.

A swallowing function with lipiodol was done, which showed that only a small amount of the contrast medium passed into the pharynx on swallowing in spite of the fact that the pharyngeal space seemed adequate.

The second tracheotomy tube was removed after 26 days. The infant experienced no further breathing difficulty. Feeding by mouth was continued but required supplementary gavage. With his tongue lengthened by the operative procedures, he was better able to grasp the nipple between the tongue and the palate. The bottle feedings aided him in exercising and thrusting his mandible forward. Solid foods were gradually introduced. Gavage feedings were finally stopped at the age of three months. He experienced no more difficulties and was discharged at the age of 13 weeks weighing 4.9 kg.

Since his discharge from the hospital, he has been followed in the Out-Patient clinic. When last seen at the age of nine months, he weighed 8.1 kg. and he had no difficulty in swallowing or breathing.

Discussion

Retruded mandible and glossoptosis giving rise to difficulty in breathing and feeding was first intensively studied by Pierre Robin in 1902,[1] and has come to be known as the Pierre Robin syndrome. Robin believed that the retracted mandible caused the floor of the mouth and tongue to be pushed back, obstructing the passage of air when the mouth is closed. The difficulty in breathing is increased because the base of the tongue presses on the epiglottis and the glottis, therefore, becomes closed. Since then, a number of other similar cases have been described with retruded or hypoplastic mandible, glossoptosis, and cleft palate. Nisenson[2] has made the last summary of cases and has listed 19 cases of hypoplasia of the mandible accompanied by glossoptosis, cleft palate, and cyanosis.

Various treatments and modifications have been suggested for the correction of the Pierre Robin syndrome which may be summarized briefly. Robin early suggested "orthostatic feeding."[1] The child is made to suck with the thorax held up straight so that he lifts his neck and propels his chin forward. Eley and Farber[3] suggested using a special brace to displace the floor of the mouth and mandible forward. Davis and Dunn[4] used a metal form to fit the upper lip. This was connected to the nursing bottle through an adjustable attachment which by degrees permitted the lengthening of the distance between the nipple and the infant's mouth. This forced the lower jaw to protrude outward.

We were confronted with a graver problem because of the additional factor of ankyloglossia. We feel certain that the infant would not have survived with the treatments

outlined for Pierre Robin syndrome alone. The operation employed by us for freeing the marked tongue-tie enabled us to convert the case into one of Pierre Robin syndrome and by gradual "orthostatic feeding" the child was able to feed and breathe without distress. The dangers of operating around an infant's oropharynx were emphasized by the two emergency tracheotomies which were necessarily done for relieving the respiratory distress.

Summary

A case of congenital ankyloglossia (tongue-tie) associated with retruded mandible, glossoptosis, and cleft palate is presented. A surgical procedure is outlined for reconstruction of the tongue-tie condition and complications and their management are discussed.

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Spanish Abstract

Anquiloglosia (Frenillo) Congénita Asociada con Mandíbula Hacia Atrás, Glosoptosis y Paladar Hendido

Se trata de un caso de frenillo congénito asociado con la mandíbula hacia astrás, glosoptosis y paladar hendido. Casos similares a los llamados síndrome Pierre Robin han sido descritos; pero en ninguno ha habido una anquiloglosia asociada. El frenillo era tan marcado que la punta de la lengua estaba agudamente doblada hacia abajo y hacia atrás y enterrada en el piso de la boca. El infante tuvo frecuentes ataques—dificultad en tragar, disnea y cianosis, los que amenazaban su vida. Para aliviar la dificultad en la respiración y en el tragar, se hicieron dos traqueotomias de emergencia.

Dos procedimientos operativos fueron hechos para corregir el frenillo. El primero puso en libertad la punta de la lengua por una incisión en la forma de V a cada lado. El segundo aumentó el largo de la lengua por medio de una incisión en forma de Z en su base donde el frenulum está normalmente situado.

Después de las operaciones, el infante mejoró gradualmente y por medio de una "alimentación ortostática" se pudo alimentar normalmente y respirar sin dificultad a la edad de tres meses.

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RHEUMATIC PNEUMONITIS IN CHILDHOOD

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EVER-INCREASING efforts to cope with the problem of rheumatic fever have imposed an obligation to be constantly aware of its diverse manifestations and of its appearance as a disease of systems other than the cardiovascular. The multifold nature of the disease is emphasized by Reich,[1] who reports such diverse findings as rheumatic peritonitis, rheumatic glomerulonephritis, involvement of such atypical joints as the sacro-iliac and astragalar, and acute rheumatic fever seen in conjunction with Reiter's disease. A report by Warren and Chornyak[2] deals with the cerebral involvement in rheumatic fever. Pulmonary lesions that occur as an expression of rheumatic infection have been of current interest, and within the past two years several comprehensive reviews have appeared in the literature. Jensen[3] points out the relationship of the pulmonary lesion to other post-streptococcal infections such as acute hemorrhagic nephritis, and differentiates the clinical picture and pathologic findings from so-called primary atypical pneumonia. Griffith et al[4] studied over 1,000 cases of rheumatic fever seen in naval personnel and found pneumonic involvement in 11.3%. In discussing the pathologic findings in two fatal cases in children, Mossberger[5] theorizes upon the allergenic basis of rheumatic pneumonitis and looks toward possible immunologic protection against rheumatic fever. The most recent work is that by Seldin et al,[6] who report the findings in six autopsied cases of rheumatic pneumonitis, only one of which occurred in a child under 12 years of age. It is the purpose of this report to add the clinical and pathologic findings in six cases of acute rheumatic pneumonitis, all of which occurred in children eight years of age or younger, and to demonstrate that the characteristic interstitial pneumonitis can be of such extent as to be a major contributing factor if not the actual cause of death in many fatal cases of acute rheumatic fever.

HISTORICAL REVIEW

Although Burnet[7] claims precedence in the description of rheumatic pneumonitis, evidence seems to indicate that Stoll[8] gave the first description in speaking of "rheumatic peripneumonia" in 1788. Early references in the English literature are attributable to Fuller[9] and Garrod.[10] The revival of interest began with the work of Rabinowitz[11] in 1926, followed by McClenahan and Paul[12] several years later. Intensive study in the pathogenesis of the pulmonary lesions and the overall pathologic picture is indicated in the work of Gouley, both in conjunction with Eiman[13] as well as by himself.[14,15] Tragerman[16] presented another brief study of the condition in 1936. But it was the work of Masson, Riopelle, and Martin[17] that was the starting point for a lively controversy over the specificity of the pathologic lesions encountered in rheumatic pneumonitis. Masson first describes the peculiar granulomatous lesions, which were called "bourgeons conjonctifs," but are now given the name of their discoverer. His conclusions were that the lesions constituted a definite specific entity, and he was supported in his belief by the preceding

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work of Gouley[15] and Tragerman.[16] However, Epstein and Greenspan,[18] in a study of 45 fatal cases, in which 14 deaths occurred in the initial attack of rheumatic fever, followed the various stages of pathologic development and concluded that the pulmonary picture should be considered as "characteristic, though not specific." There followed the work of Neubuerger and his colleagues,[19] who described in detail the microscopic picture of rheumatic pneumonitis, and gave the name "Masson body" to the distinctive granuloma, which they felt to be the pulmonary equivalent of the Aschoff body in the myocardium. Herbut and Manges[20] were able to demonstrate these lesions in such diverse conditions as bronchiectasis, tuberculosis, lung abscess, and organizing pneumonia; and felt, therefore, that they must not be specific. The most recent opinion seems to be that the lesions are sufficiently characteristic to constitute diagnostic criteria in the face of other pulmonary changes, especially the vascular lesions which are characteristic of rheumatic infection throughout the body.[5, 6]

Source of Material and Scope of Observation

We have had the opportunity to observe six cases of rheumatic pneumonitis on the Pediatric Service at Shreveport Charity Hospital during the period from December 1944, to April 1947. Five of these cases were confirmed at autopsy, while the clinical course of the sixth was so characteristically similar to the others as to warrant the diagnosis in this case as well, although necropsy permission was not granted. The patients ranged from 2½ to eight years of age, and presented what was felt to be the initial rheumatic attack in all but one case. All six patients were Negro children. A brief summary of the case reports is presented in Table I.

Discussion and Correlation of Findings

Clinical Course: In each of the six cases reported here, the clinical course was that of a severe and rapidly fatal infection. Two died as early as the sixth hospital day, and only one lived for slightly over a month. All but Case 3 were apparently in their first rheumatic attack. The severity of the clinical picture is in accord with the findings of Seldin et al[6] and Jensen,[3] the latter reporting a case of a 19-year-old sailor who died within 15 days from the onset of his first rheumatic episode, 30 days after his upper respiratory infection. Epstein and Greenspan[18] report 14 cases which were fatalities in the first rheumatic attack, and both of the cases reported by Mossberger[5] were of comparable severity to ours. Seldin[6] also comments on the transient nature of the physical findings, and their diversity is well shown in the work of Myers and Ferris.[23] We are unable to find any agreement of symptomatology and physical findings with the extent and severity of the condition. One must be constantly aware of the possibility that rheumatic involvement of the lungs exists, and of the grave prognostic import that such involvement carries.

Pathologic Observations: Grossly, we were impressed with the widespread involvement encountered throughout the lungs, although the gross picture itself is not too characteristic. The mottled appearance and diffuse nodular lesions have been well described by Neubuerger[19] and Tragerman.[16] Microscopically, the lesions seen in the lungs may be divided into four main types:

(a) Granuloma: This lesion, described by Masson[17] and given his name by Neubuerger[19] was at first considered to be the specific lesion of rheumatic pneumonitis, until Herbut and Manges[20] demonstrated its occurrence in many other conditions. However, although not specific, it is certainly characteristic enough when seen with other signs of rheumatic infection. The lesion is ovoid or round in shape, and is composed of many cells with flat,

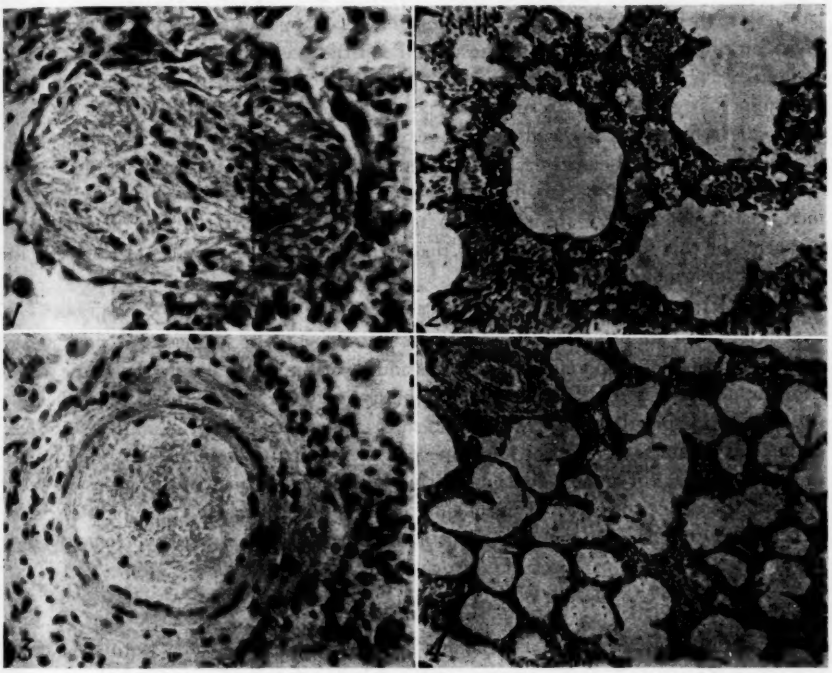
TABLE I

Case No.	Age (yr.)	Sex	Pertinent History	Cardiac Findings	Pathologic Lung Findings
1 (V.H.)	7	F	U.R.I two weeks before admission. Vomiting and fever 8 days' duration; abdominal pain; cough productive of thick mucoid material. Suggestive history of vague joint pains. Expired on 17th hospital day.	Enlarged to percussion. Apex beat 1 cm. lateral to mid-clavicular line. Blowing systolic and rumbling diastolic murmur at apex. Harsh systolic and diastolic murmur in third and fourth interspace lateral to sternum on left.	Left—300 gm. Right—340 gm. Gross: mottled bluish red discoloration. Small scattered areas of consolidation on cut surface. Micro: Diffuse interstitial pneumonitis with marked perivascular changes and hyaline membrane formation in alveoli.
2 (D.S.)	8	M	Diffuse swelling of face, hands, then ankles and abdomen. Two weeks' duration. Increasing dyspnea; frequent, nonproductive cough. Expired on 15th hospital day.	Enlarged to percussion. Systolic apical murmur transmitted to axilla.	Left—250 gm. Right—360 gm. Gross: mottled grayish red to dark red areas of firmness throughout both lungs. Micro: Fibrinous exudation with focal fibrinoid alveolitis and hyaline membrane formation. Many vascular lesions typical of rheumatic involvement.
3 (R.S.)	7	M	3 previous admissions with cardiac decompensation. Initial attack, one year previously. Abdominal pain and sore throat on final admission. Some dyspnea but no cough or chest pain. Expired on 15th hospital day.	Marked cardiac enlargement with apex beat diffuse, maximal intensity in sixth interspace at axillary line. Harsh blowing systolic murmur at apex.	Left—280 gm. Right—340 gm. Gross: Numerous dark bluish-red areas scattered throughout. Micro: Marked thickening of alveolar septae with proliferation of spindle cells and round cells with some fusion and giant cell formation. Areas of polymorphonuclear infiltration are seen, as are foci of alveolar necrosis.
4 (P.D.)	5½	F	Joint pains of one week's duration, migratory in nature. Easily fatigued, slight anorexia. No previous attacks. Expired on 33rd hospital day.	Upper limits of normal size. Thrill palpable in third interspace to left of sternum. Soft blowing systolic murmur in area of thrill. Systolic and diastolic murmur at apex. Pericardial friction rub.	Permission for autopsy denied.
5 (W.C.)	6	M	U.R.I.—4 weeks previously. Migratory polyarthritis two weeks' duration. Pain left chest, 1 week. Expired on 6th hospital day.	Enlarged to percussion. Apex beat in anterior axillary line. Loud systolic murmur over entire precordium with maximal intensity at apex.	Left—250 gm. Right—270 gm. Gross: Somewhat solid, with dark-bluish red nodular areas throughout, leathery in consistency. Micro: Many granulomata (Masson bodies) with widespread periarterial involvement.
6 (B.A K.)	2½	F	Shortness of breath, pain in left chest, two weeks' duration. Expired on 6th hospital day.	Enlarged to percussion. Harsh blowing systolic murmur at apex.	Gross: Red and bluish-red mottling throughout. Micro: Thickening of alveolar walls with proliferation of septal cells. Hyaline membrane formation. Arteriolar lesions of rheumatic infection.

spindle-shaped nuclei, these cells showing marked tendency toward polarity. There is a loose fibrillary and collagenous stroma. The granuloma is covered with flattened or cuboidal cells similar to the septal cells lining the alveolar walls. These granulomata are seen within the alveolar ducts, often extending into the alveoli themselves. They may be considered as the pulmonary counterpart of the Aschoff body in the myocardium, although the latter appear in the interstitial connective tissue. A typical Masson body is shown in Figure 1.

(b) Focal fibrinoid necrosis and alveolitis, with hyaline membrane formation: The alveolar walls themselves show focal areas of necrosis, with fine peppering of polynuclear cells, differing in their distribution in ordinary bacterial pneumonia. The alveoli may be filled with hyaline-staining material, or may show compression of this material against the alveolar wall with formation of a hyaline lining membrane. Such involvement is shown in Figure 2.

(c) Arteriolitis: This is the lesion so characteristic of rheumatic infection in other organs, and is well demonstrated by the fibrinoid swelling of the vessel wall with poly-



PATHOLOGIC LESIONS ENCOUNTERED IN RHEUMATIC PNEUMONITIS

FIG. 1. Granuloma or "Masson Body."
FIG. 2. Focal Fibrinoid Necrosis and Alveolitis; Note Hyaline Membrane Formation.
FIG. 3. Arteriolitis.
FIG. 4. Septal Cell Proliferation.

nuclear and lymphocytic infiltration. Von Glahn[21] has commented on the similarity of the vascular lesions in the various organs of the body, and Friedberg and Gross[22] remark on the definite resemblance between these lesions and those seen in periarteritis nodosa. A typical arteriolar lesion is seen in Figure 3.

(d) Septal cell proliferation: This pathologic change took the form of marked swelling and proliferation of the cells of the alveolar septæ, with formation of an incomplete lining, as described by Mossberger.[5] The appearance of this involvement is seen in Figure 4.

Roentgenologic Findings: The roentgenologic appearance shows no appreciable difference from that seen in pulmonary congestion, except for the transient nature of the

findings. The fleeting character is very well shown in the works of Griffith[4] and Seldin.[6] As the latter points out, the picture is of value chiefly in differentiation from bacterial and primary atypical pneumonic consolidations.

Therapeutic Efforts: The efforts at therapeutic control are only mentioned to point out their futility to date. Myers and Ferris[23] have shown the ineffectiveness of salicylates in controlling the pleural and pulmonary involvement in rheumatic fever, a fact borne out by their use in five of our six cases without any apparent improvement. Sulfadiazine was administered to two of the earlier cases, before the work of Swift et al,[24] together with our own experience, caused its discontinuance because of the deleterious effects. In two of the later cases, there was suspicion that sulfonamide therapy had been used by the family physician prior to admission to the hospital. Penicillin was given to three of the six cases without effect; this result is comparable to the findings of Rantz,[25] Watson,[26] Foster,[27] and their respective co-workers. Because of the possibility of an explanation of the pathogenesis on an allergenic basis,[4] it was decided to give one patient (Case 4) a trial regimen with B-dimethylamino-ethyl-benzhydryl ether (benadryl), following the work of Feinberg.[28] The patient received 50 mg. orally three times daily for 12 days without effect other than increased drowsiness. We are inclined to agree with Ratner[29] concerning the limitations of agents of this sort. We must admit that at present there is no therapy available for rheumatic pneumonitis.

Summary

Sufficient data are presented to indicate the pathologic entity of rheumatic pneumonitis and its position of importance as an outstanding cause of death in rheumatic fever, either primarily or secondarily. In each of the five autopsied cases, there was sufficiently severe and widespread pulmonary involvement to suggest that the pneumonitis led the way to the fatal termination, either by impairment of the respiratory system alone, or by further adding to the load of an already dangerously impaired cardiac mechanism. If, as Stewart[30] has said, the danger of bacterial pneumonia is such an acute one as a precipitating factor in heart failure, how much more perilous is the existence of a severe involvement which appears to be part and parcel of the rheumatic picture as a whole.

Conclusions

Six cases of fatal rheumatic pneumonitis in childhood are presented, with the autopsy findings in five. In each of the six cases, it was felt that the clinical course and pathologic findings justified the conclusion that the rheumatic pneumonitis was an outstanding, if not the prime, cause of death.

During the course of rheumatic fever in childhood, especially in the initial attack, one must be constantly alert in an effort to discover the presence of widespread pulmonary involvement, as it would appear to have a grave prognostic significance.

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SPANISH ABSTRACT

Pneumonía Reumática en La Niñez

El conocimiento de las manifestaciones de la fiebre reumática en síntomas de órganos además del cardiovascular es esencial. Se ha observado en los pulmones una pneumonitis intersticial difusa caracteristica, la cual parece amenudo suficientemente severa para considerarsele un factor contribuyente si no la verdadera causa primaria de muerte.

El exámen microscópico revela cuatro tipos de lesiones: Granuloma (o cuerpo Masson); necrosis fibrinoide focal y alveolitis con formación de membrana lialina; arteriolitis; y proliferación de la célula septal.

Seis casos de fiebre reumática aguda, con complicaciones pulmonares severas, están presentados con el informe clínico y patológico. Los pacientes fueron negros, variando en edad de 2½ a ocho años. El curso clínico de cada uno fué una infección fatal rápida y severa. Los esfuerzos terapéuticos fueron en vano.

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JUVENILE RHEUMATOID ARTHRITIS

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IN 1897, Still[1] separated juvenile rheumatoid arthritis into two types: (1) chronic rheumatoid arthritis similar to the adult form of the disease; (2) a less frequent type with the same joint manifestations, associated with generalized lymphadenopathy, splenomegaly, hepatomegaly, and sometimes adhesive pericarditis or other visceral lesions, which has commonly been referred to as Still's disease.

This concept, that Still's disease is a separate entity, has been responsible for much confusion and also for the belief that this is a grave, intractable, unusually crippling form of the disease. We recognize today that there is no justification for this division, since these associated pathologic findings are a part of the disease process of rheumatoid arthritis, especially in children where age is the factor responsible for considerable modification of the disease. It would be preferable to discard the term "Still's disease" and instead, refer to the disease as juvenile rheumatoid arthritis. We must also realize that the pessimistic outlook which has been commonly attached to this disease in the past is not warranted and that severe deformity is the infrequent, rather than the usual, result of the disease. Colver[2] was the first to state that crippling was infrequent and that complete recovery was not uncommon. Recently, Coss and Boots[3] and Pickard[4] have published excellent studies of juvenile rheumatoid arthritis.

Since 1934, we have had the opportunity to treat and observe 28 cases of typical juvenile rheumatoid arthritis, which began before the age of 12. Certain cases presented difficulty in the differential diagnosis of this disease from rheumatic fever and tuberculosis. Three patients required observation for periods up to six months and one patient was followed for a period of 5½ years before we were certain that rheumatoid arthritis and not rheumatic fever was the correct diagnosis. These four patients had fleeting joint complaints, fever and cardiac findings (harsh systolic murmurs in all four patients and pericarditis in two patients) which several examiners felt were of sufficient degree to warrant a diagnosis of rheumatic fever. Later, the disappearance of the murmurs and the eventual occurrence of persistent joint changes and other constitutional signs helped to confirm the diagnosis of rheumatoid arthritis. A trial with salicylates, the predominance of either cardiac or joint lesions, the presence of constitutional signs (weight loss, generalized lymphadenopathy, splenic or hepatic enlargement), and sometimes only the lapse of a considerable period of time, help to differentiate the two diseases.

In three patients, rheumatoid arthritis occurred as a monarticular involvement of a knee joint. It was possible in all three patients to make the correct differential diagnosis from tuberculosis with the help of negative tuberculin tests (1:100), aspiration of fluid from the involved joint with negative culture tests and guinea pig inoculations, and the improvement of the joint after treatment for rheumatoid arthritis.

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The average age at onset in our group of 28 cases was six years. The two earliest cases occurred at 12 months of age. The ratio of females to males in this group was 2.5 to 1 (20 females to 8 males). Other observers, Clover,[2] Coss and Boots,[3] have found the ratio of females to males as high as 5 to 1, while some (Still,[1] Pickard[4]) have reported the ratio to be only 1.5 to 1.

Precipitating Factors

Preceding Respiratory Illness—Ten cases (35.7%) had a history of a preceding respiratory infection and seven cases showed a significant number of Str. hemolyticus present on nasopharyngeal culture. Coss and Boots[3] reported an incidence of 32 cases (57%) and Pickard[4] 16 cases (45.7%) in their series of respiratory infection associated with the onset of arthritis.

Two patients in our group gave a definite history of aggravation of their arthritis after removal of foci of infection during the prodromal period of the disease. In six patients, surgery was performed on the upper respiratory passages after the arthritis was well established, with apparent beneficial effects on the arthritic process. No evidence of aggravation was noted in these patients.

Coss and Boots[3] determined the antistreptolysin titer in 24 cases and considered the median figure obtained (250) significantly higher than normal (100). In our cases, the antifibrinolysin titer did not give significant results.

Trauma—Injury to the knee joint was a significant factor in the onset of arthritis in three children (10.7%) in our group. Two cases remained monarticular and one developed multiple joint lesions after a period of several months. Pickard[4] felt that trauma was a definite factor in the onset of arthritis in seven cases of his series (20%).

Degree of Involvement, Duration and Character of the Disease

Degree of Involvement—Pickard[4] has recommended a practical classification of the disease process as mild, moderate, or severe, depending on the duration of the disease, the degree of joint involvement and constitutional reaction, associated visceral lesions, and the degree of residual joint deformity. Of his 35 cases, 11 were classified as mild, 19 were moderate, and five were severe. In our group of 28 cases, using the same factors for comparison, seven cases were mild, 17 were moderate, and four were severe. Of the four severe cases, two patients have died and the other two show extensive, hopeless crippling.

Joint Involvement in 28 Cases

Joints	*Involved (Active Phase)*	*Residual Change*
Knee	28*	7†
Hand	18	5†
Elbow	13	9†
Wrist	14	6†
Ankle	15	2†
Cervical Spine	8	4
Hip	7	4†
Shoulder	6	4†
Foot	4	2
Jaw	3	2

* Monarticular involvement of knee in three cases.

† Residual figures may not all be permanent, as three active cases are included.

CONSTITUTIONAL REACTION IN RHEUMATOID ARTHRITIS

Pertinent Findings	*Frequency* (28 cases)
Anemia	15
Weight loss	15
Fever	12
Lymphadenopathy	5
Splenomegaly	4
Hepatomegaly	3
Interference with Skeletal Development	4
Cardiac Involvement	2
Iritis	1
No constitutional reaction	9

Interference with proper skeletal development and growth was observed in four of our cases. All four cases had fusion of two or three cervical vertebræ, two cases revealed shortening of the extremities, and one case exhibited shortening of his fingers. Coss and Boots[3] reported that some disturbance of the skeletal pattern occurred in 22 of the 56 cases (39%) studied.

Duration of Activity—Colver[2] reported the maximum period of activity was seven years and also stated that no reactivation of the disease occurred after a terminal quiescent period of 18 months had elapsed. However, our experience and also that of other observers has not been completely in accord with these statements.

The average duration of the disease in our group has been four years, but two of the three patients still active have had a duration of over eight years. In 23 of the 28 cases, there was only one well-defined period of activity. However, the other five patients had a total of 14 distinct periods of activity. One patient had four definite periods, after he had apparently reached a state of quiescence for periods of from six months to 3½ years. Two patients had three distinct periods of activity after quiescent intervals of 1½ and three years, and four and 4½ years respectively. The remaining two patients in this group who had multiple periods of activity, had a recurrence of activity after a quiescent state of 1½ and two years. The latter patient, who had completely recovered from his first attack of rheumatoid arthritis, suffered reactivation of the disease after a quiescent state of two years and had continuous progression of the disease until he expired three years later.

In three of the five patients who had more than one period of activity, respiratory infection appeared to be the factor responsible for reactivation in each instance.

Coss and Boots[3] reported that 12 cases of their group had a duration of seven years or more, and that one patient had six periods of activity in a 23-year interval. Pickard[4] found nine patients who suffered a second attack of rheumatoid arthritis after periods of quiescence ranging from two to eight years and observed that infection appeared to be responsible for the "recrudescence" in five of the nine instances.

TREATMENT

Treatment has been difficult to evaluate, but several procedures have proven to be essential. Complete bed rest is the most important part of treatment and must be maintained until all evidence of activity (whether it is systemic or joint activity) has subsided. The child is permitted to sit up in bed at mealtime and for diversional recreation as the disease improves. A pillow or blanket roll is used at the foot of the bed to support the weight of the bedclothes. Since the child naturally increases the use of his joints as the

disease improves, intensive physiotherapy is not necessary. However, we have felt that the use of infra-red heat and mild muscle massage are valuable. The infra-red lamp was used twice daily for 15 to 20 minutes on the painful joints, at a distance of from two to three feet (where it feels comfortably warm). Massage must always be mild and is applied only to the muscles. Passive motion and later, carefully graduated active motion, are permitted, but never to the degree of producing pain. The child will voluntarily increase the use of his joints as the pain and inflammatory process subside.

We have employed routinely a high caloric and high vitamin diet in these children, since many of them have been malnourished. Transfusions have been of definite benefit to the acutely ill patient. Small amounts of blood are given at weekly intervals until improvement occurs.

Orthopedic measures are useful when there is acute inflammation and muscle spasm present. The most valuable plaster splints have been the posterior leg splint and the cock-up splint to immobilize the knee and wrist respectively and thus relieve the pain and muscle spasm. Splints are removed several times daily to permit mild physiotherapy and mild motion of the joint. X-ray therapy has been used in small doses, several times a week in some of our patients to alleviate persistent pain. Salicylates are employed to relieve pain and we have found it unnecessary and undesirable to use opiates in any form.

Foci of infection were removed in six patients with apparent benefit and no aggravation of the disease process. This may be performed during the active phase of the disease if there is definite evidence of infection present in the respiratory tract. Two patients in this group did have exacerbation of joint involvement when tonsillectomy was performed during the prodromal phase of the disease.

Gold salt therapy was employed in the form of myochrysine in half of our group. A dose of 10 mg. was given at weekly intervals until improvement or a mild reaction occurred. The average total dose in this group was 300 mg. and the highest dose was 910 mg. Only two mild reactions (dermatitis) were encountered. Because of the small number of patients and the rapid spontaneous improvement of some, it was felt that we could not properly evaluate the results of gold salt therapy. However, we do feel that this form of therapy should be employed much earlier in treatment, and not be delayed until all other measures have failed to produce improvement.

A few patients were given injections of foreign protein, streptococcal vaccine, and intravenous typhoid vaccine when we did not think it advisable to use gold. We do not feel that manipulation or surgical procedures are indicated in the treatment of this disease.

	Results in 28 Cases	*Pickard*
(1) Complete Recovery	12 (42.8%)	14 (40%)
(2) Mild residual joint deformity*	6 (21.4%)	2 (5.7%)
(3) Moderate residual joint deformity*	3 (10.7%)	2 (5.7%)
(4) Severe residual joint deformity*	2 (7.1%)	7 (20%)
(5) Death	2 (7.1%)	3 (8.6%)
(6) Still active	3 (10.7%)	7 (20%)
(a) mild	1	1
(b) moderate	2	4
(c) severe	0	2

* Joint deformity has been tabulated as suggested by Pickard[4] in his report: (1) Minimal deformity is the major impairment of a minor joint or minor impairment of a major joint. (2) Moderate deformity is the major impairment of a major joint, without loss of function of the involved limb. (3) Severe deformity is the loss of use of an extremity or impairment of locomotion.

Two patients died and the pathologic reports were as follows: (1) Severe crippling arthritis, marked inanition, ascites, adhesive pericarditis, endocarditis, pulmonary tuberculosis, decubitus ulcers.' (2) Severe crippling arthritis, septicemia due to Staph. aureus hemolyticus, pericarditis, splenitis, hepatitis, nephritis, and multiple abscesses.

Summary

Twenty-eight cases of juvenile rheumatoid arthritis have been observed over a period of 14 years. The results prove that a high proportion of these patients recover completely and that the older pessimistic prognosis is not justified. The etiologic factors, the clinical characteristics, the differential diagnosis, and treatment of the disease have been discussed. We have attempted to correlate our findings with the reports of several other observers[2-4] to make possible a more comprehensive review of this important disease of children.

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Spanish Abstract

Artritis Reumatoidea Juvenil

La esplenomegalia, hepatomegalia, linfadenopatia generalizada y algunas veces otras lesiones viscerales son partes íntegras del desarrollo de la artritis reumatoidea. Nos parece que esta enfermedad debría de llamarse "Artritis Reumatoidea Juvenil" y no "Enfermedad de Still," la que implica una entidad separada y la forma grave, intratable, que generalmente tulle, de la enfermedad. Algunas veces es difícil diagnosticar esta enfermedad de la fiebre reumática. La diagnosis de tres casos de artritis reumatoidea monarticular provenientes de la tuberculosis fueron menos difíciles.

La enfermedad les vino a nuestros dos pacientes más jóvenes a la edad de 12 meses. La proporción de mujeres a hombre en nuestros 28 pacientes fué 2.5 a l. Infección en el tracto respiratorio y complicación de las coyunturas fueron factores significantes al principio. La enfermedad fué suave en siete, moderada en 17, y severa en cuatro casos. Las coyunturas frecuentemente afectadas fueron las rodillas, las manos, los codos, las muñecas y los tobillos. Muy amenudo cuando los codos, espina cervical, caderas y hombros estaban afectados había algun daño residual. No hubo reacción constitucional en nueve; fiebre, anemia y pérdida de peso fueron más frecuentes en los otros 19 pacientes. La linfadenopatia generalizada estuvo presente en cinco, la esplenomegalia en cuatro, la hepatomegalia en tres, y la inferferencia del desarrollo del esqueleto normal en cuatro casos.

La duración media del desarrollo de la enfermedad en nuestro grupo fué de cuatro años, pero dos pacientes (aún activos) la han tenido por más de ocho años. En cinco pacientes hubieron múltiples períodos de actividad, con reactivación después de períodos de aparente reposo de algunas veces hasta cuatro y 4½ años de duración.

Es difícil de evaluar el tratamiento; pero varios procedimientos han dado buenos resultados. Completo descanso en la cama se debe de guardar hasta que desaparezca toda actividad. Fueron empleados una dieta alta en calorias y vitaminas y la fisioterapia. Las transfusiones, medidas ortopédicas, terapia de rayos X, eliminación de infecciones de foco, y la terapia de sal de oro resultaron de beneficio. La terapia de oro consistió en miocrisina, administrada 10 mg. cada semana hasta verse un mejoramiento o una reacción suave. Nos parece que esta terapia debe de ser usada en el tratamiento y no hay que esperar hasta que otras medidas hayan fracasado. Solamente se encontraron dos reacciones suaves (dermatitis) en los 14 pacientes a quienes se les dió la terapia de oro.

El concepto pesimista asociado con esta enfermedad necesita revisión, pues los resultados en este grupo son: completo restablecimiento 12, residuo de coyuntura mínimo en seis, residuo de coyuntura moderado en tres, deformidad de coyuntura residual severa en dos, muerte en dos, y tres que todavía están padeciendo. Un total de 18 (64%) han tenido un restablecimiento excelente de esta enfermedad.

40 North St.

Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

EASTERN AREAL MEETING
Buffalo, N.Y.
April 29-May 2, 1948

SUMMARY

The scientific program of the meeting was somewhat in the nature of a postgraduate course, designed to bring the practicing pediatrician up-to-date on the various subjects presented. Much experimental data was presented to support new beliefs. Four of the six sessions consisted of symposia, the two others included a variety of timely topics. The opening paper of the meeting was given by Allan M. Butler entitled, "Management of Diabetic Acidosis," in which he discussed the basic electrolyte disturbances in this disease as related to acid-base imbalance. He stressed the need for giving both extracellular and intracellular electrolytes in the repair solutions and pointed out that saline solution should be adjusted so that the Na and Cl are in equal osmolar concentration to that of the plasma. Wolf W. Zuelzer presented the second paper on "Liver Deficiency Anemia in Children." He emphasized that this condition is certainly not rare and that probably many of these cases of megaloblastic anemia in infants were being overlooked. The clinical syndrome which he has so well described was presented and the possibility of a dietary factor as etiologic was discussed. The rapidity of the bone marrow response to folic acid and liver extract was clearly brought out. The final paper of the first session was presented by Harold W. Dargeon, entitled, "Newer Agents in the Treatment of Childhood Cancer." This included a large group of patients with leukemia. The effect of radioactive isotopes, nitrogen mustard, carbomates (urethane), and folic acid and allied substances on 61 cases was presented. With the use of various of these substances remissions were obtained but so far cures were not produced by any.

The second session was given over to a symposium on "Metabolic Disturbances." Katharine Dodd opened the session with a discussion of various hypocalcemic states seen in pediatric practice. She pointed out that the so-called rachitic tetany makes up a relatively small percentage of the total incidence and emphasized the frequency of hypocalcemia in post-acidotic (diarrheal) states. The large variation in clinical symptomatology with hypocalcemia as presented must renew wide interest in infantile tetany. A. Ashley Weech gave the second paper in this symposium on "Disturbances in Protein Nutrition" in which he correlated the relationship of salt intake and levels of serum protein to the development of edema. The correlated changes in blood and plasma volumes and liver function were presented. The third paper entitled, "Lipid Disturbances," was presented by L. Emmett Holt, Jr. A list of the basic causes of disorders of fat metabolism was given and striking evidence was presented to show that in the common causes for steatorrhea in children—celiac disease, cystic disease of the pancreas, infantile diarrhea, and prematurity—better fat absorption occurred on high fat intakes than on low intakes. This conclusion was contrary to generally accepted belief but considerable

experimental data was presented for its support. The final paper on this symposium was given by Alexis F. Hartmann on "Disturbances in Carbohydrate Metabolism" in which considerable attention was given to the intermediary metabolism of carbohydrates and how it is related to clinical ketosis. A very instructive movie on the relationship of some of the members of the vitamin B complex to the intermediary metabolism of carbohydrates was shown. This entire symposium proved to be one of the highlights of the meeting.

The third session was a symposium on "The Cardiovascular System." The first paper was by John Gregory on "Experimental Periarteritis and Rheumatic Lesions" in which he emphasized, after showing experimental data, that rheumatic fever is a disease of hypersensitivity. May G. Wilson then discussed "The Diagnosis and Prognosis of Rheumatic Fever." She pointed out among many other things that (1) 60% of her cases were living over 30 years after the onset of their disease, (2) the age of onset affected the survival period, (3) 55% of her cases have survived to age of 40 years, (4) that the prognosis in the group before the year 1920 is no different than in the group after 1920. The next paper in the group was on "Diagnosis and Prognosis of Congenital Disease of the Heart and Vessels" given by Helen B. Taussig. The following lesions were discussed, patent ductus, coarctation of aorta, aortic ring, tetralogy and cyanotic group, truncus, and transposition of great vessels, giving pertinent clinical facts, X-ray diagnosis and surgical prognosis. As a companion piece to this paper Roy E. Siebel discussed the diagnosis of some of the congenital heart lesions by cardiac catheterization. X-ray films and diagrams were shown to demonstrate the different heart chambers and the value of intracardiac blood oxygen content and blood pressure determinations in diagnosing the various anomalies. The final paper of the symposium was presented by Mitchell I. Rubin on "Myocardial Failure in Infancy and Its Management," in which he pointed out that interstitial myocarditis in infancy is by no means a rare disease. The cases presented were divided into two groups, one the so-called "non-infection" group in which no evidence of preexisting or coexisting infection could be found, and the other, the "infection" group where evidence of active or preexisting infection was demonstrable. The "non-infection" group were mostly under six months of age, the course was rapid and the death rate high. Enlarged heart, enlarged liver, gallop rhythm, X-ray evidence of pulmonary congestion, rapid pulse out of proportion to temperature, cyanosis, and electrocardiographic changes were diagnostic features. In those with active infection, especially in the lungs, the diagnostic signs were less certain. The need for more accurate objective signs in the diagnosis of cardiac failure in infancy was stressed. The electrocardiographic pattern and microscopic lesions were shown and the various possible etiologic factors were presented. Treatment was discussed, the effectiveness of water restriction and diuretics in conjunction with digitalis was emphasized in the management of myocardial failure.

The fourth session was on the "Management of the Child with Chronic Disease." Charles A. Janeway presented the subject of "Nephritis and Nephrosis." Among other things he discussed the various mechanisms involved in induced diuresis in nephrosis, and emphasized the value of salt restriction during edema. He pointed out the psychologic implications of the disease and recommended home care where possible both for its influence on the emotional status of the child and the prevention of infection. The second presentation, "Management of Orthopedic Problems in Pediatrics (Congenital Deformities)," by William T. Green included a long list of conditions wherein the pediatrician plays a major role in diagnosis and possibly treatment. He stressed the importance of early diagnosis in influencing the prognosis in such cases as congenital dislocation of the hip, club foot, torticollis, and others and gave a description of the therapeutic procedures. L. Maxwell Lockie then discussed "Infectious Arthritis" in children. He pointed out that the disease was not too uncommon and generally had a good prognosis. He emphasized that treatment should be of a broad general nature and noted that gold was an effective therapeutic agent. The final paper of this session was on "Asthma (Chronic Form)" and was presented by Jerome Glaser who emphasized the importance of detailed histories for patients with this disease. He discussed the influence of the various exciting nonspecific factors such as exercise, exposure to cold, infection, emotional upsets on the disease and emphasized that while these play some etiologic part, they were secondary to specific antigenic stimulation and every effort should be made to determine them. The long term point of view in the management of these cases was stressed noting that every etiologic possibility should be controlled.

The fifth session was devoted to some aspects of "The Central Nervous System." R. Walter

Schlesinger presented "Specific Diagnostic Methods in the Virus Encephalopathies" in which he discussed the various laboratory diagnostic methods and showed examples of their value in elucidating certain clinical conditions. He pointed out that all virus encephalopathies have at some time a pleocytosis in the spinal fluid. The second paper was given by Herbert Jasper entitled "The Use of the Electroencephalograph in Neurological Diagnosis in Children." Dr. Jasper pointed out that disturbances in the normal pattern of electrical activity of the brain were produced by local brain lesions such as those due to a head injury and brain tumors, as well as more generalized disturbances produced by encephalitis, degenerative diseases and following anoxia or birth trauma. He pointed out the importance of the electroencephalogram in the diagnosis of epilepsy and for use in localizing the source of epileptic discharge. He demonstrated that with detailed localization studies that a far greater number of patients may be classified as having focal epilepsy and emphasized the importance of the clinical history in helping determine the focal area. He noted that the finer disturbances in brain function such as are associated with intelligence and mental diseases do not make themselves manifest in the changes in the electroencephalogram and that the electroencephalograph is still a crude apparatus. The final paper of this session on the "Diagnosis and Management of Increased Intracranial Pressure" was given by Barnes Woodhall who discussed the hydrodynamics of intracranial pressure especially as related to brain tumors in children.

The final session of the meeting was given over to miscellaneous topics. "Pediatric Economics" was discussed by Warren R. Sisson who showed some data culled from his pediatric survey. Frederick H. Allen presented the topic of "Psychosomatic Pediatrics." He pointed out that young children in a large measure handle their feelings around bodily functions and it was only as a child grew older that he could handle feeling as feeling itself and have it unrelated to eating or sleeping or the various other bodily functions. He noted that where a bodily function is used to express feeling one is likely to have disturbance in that function. The final paper of the meeting was on B.C.G. presented by Conrad H. Birkhaug who gave a dramatic account of the development and early experimentation with this vaccine. He told of the Lübeck trial and the vindication of Calmette's vaccine. He presented data showing the value of B.C.G. as a prophylactic agent against tuberculosis and urged its general use in this country under controlled condition to tuberculin negative individuals (especially those subject to exposure).

MITCHELL I. RUBIN, *Chairman*
Scientific Program Committee

1. PARENTERAL THERAPY IN DIABETIC COMA

BY ALLAN M. BUTLER, M.D., BOSTON, MASS.

The quantitative appraisal of desirable parenteral fluid therapy of patients suffering the dehydration and starvation of diabetic coma is made possible by the metabolic data of Atcheley and coworkers and ourselves on losses sustained by subjects going into coma and on maintenance needs during the period of parenteral therapy. These metabolic data when extrapolated to include extension of the dehydration and acidosis beyond that permitted the volunteer subjects of the experimental studies suggest the following order of magnitude for water and electrolyte repair and maintenance needs/kg. body weight during the first 24 hrs. H_2O — 150 cc.; Na — 5.5 mEq.; Cl — 4.5 mEq.; K — 4 mEq.; Mg — 0.7/mEq.; P — 1.1 mEq. For the past two years our pediatric service at the Massachusetts General has based its therapy on such replacement needs with satisfying results, by giving the following solutions as required until nourishment could be given orally. First, initial hydration to improve circulation and renal function: 75 mEq. Na, 50 mEq. Cl, 25 mEq. lactate and 30 gm. glucose/1. at rate of 20 cc./kg./45 min. Second, multielectrolyte solution containing 30 mEq.Na, 22 mEq. Cl, 20 mEq. lactate, 20 mEq. K, 5 mEq. P, and 50 gm. glucose/1. at 1cc./min. in infants up to 5 cc./min. in adults as indicated by water needs of 100 to 150 cc./kg./24 hours.

Even if such need should be increased by 50%, the replacement therapy would demand only 7 to 8 mEq. of Na/kg. This is less than half the amount advocated by those who base their therapy on calculating the specific deficit in sodium either by determining the decrease in plasma bicarbonate concentration or by averaging amount of administered sodium /kg. necessary to return the

decreased plasma bicarbonate concentration of a group of cardiacs, nephritics and diabetics to normal and in addition to giving the thus specified amounts of sodium bicarbonate or lactate also give liberal amounts of physiologic saline. Both calculations embrace the false assumption that "alkali" must be added to correct the bicarbonate deficit, when actually insulin and fluid therapy to a considerable extent correct the acidosis by removing ketone and other acids, thus increasing the bicarbonate without addition of "alkali." Moreover, Peters et al have shown that the decrease in plasma sodium and chloride concentrations in severe diabetic coma are proportional and that the low plasma HCO_3 and pH are, therefore, due to added acid rather than sodium deficit. Physiologic repair of extracellular sodium deficit would thus appear to be satisfied by administration of sodium and chloride in the ratio pertaining in extracellular fluid; namely, 1.3 to 1. If the repair hydration therapy thus provides sodium for extracellular fluid, the elimination of the elevated plasma acids of coma should free sodium for return to cells.

Unfortunately the metabolic data to determine the ultimate disposition of the large amounts of sodium that frequently have been administered are not available. However, data do show the serum pH may be elevated to alkalotic levels; a result that would appear undesirable to have follow the immediately preceding state of acidotic depletion. Indeed it has been remarked that all diabetic coma deaths in one clinic using large amounts of sodium lactate occurred after the acidosis had been corrected.

On the other hand infusion of so-called "physiologic saline" as the only hydration therapy, while limiting the excessive invasion of tissue cells by sodium ignores the serious acidosis and the exhausting Kussmaul breathing. Thus "isotonic saline" appears to be contra-indicated as initial therapy lest the hypertonicity of the Cl^- increase the acidosis. Indeed for most clinical conditions physiologic saline is unphysiologic.

The serious sequalæ to giving large amounts of sodium as alkali or saline to potassium depleted patients have been demonstrated in experimental animals, infant diarrhea, human cholera, and diabetic coma. In the last two conditions, there has resulted a syndrome of muscle weakness including respiratory and cardiac failure. This syndrome has been associated with marked lowering of serum potassium concentration and has been relieved by the administration of potassium.

As indicated by extremely low serum in organic phosphorus levels persisting throughout the period of therapeutic recovery from coma and Guest and Rapoport's demonstration of intracellular lack of phosphorus there is also a need of phosphorus during the period of parenteral therapy. Balance studies and the low serum magnesium concentrations encountered during the therapy suggest a need of magnesium.

Finally, the addition of potassium and phosphorus to the parenteral therapy permits early and certain provision of such glucose as is beneficial in accelerating glucose metabolism, lessening ketosis by satisyfing caloric needs and replenishing tissue glycogen without risk of lowering the plasma concentrations of these elements, retarding their replacement in tissue and predisposing to the potassium deficiency syndrome.

2. LIVER DEFICIENCY ANEMIA IN CHILDHOOD

BY WOLF W. ZUELZER, M.D., DETROIT, MICH.

(See Summary)

3. NEWER AGENTS IN THE TREATMENT OF CHILDHOOD CANCER

BY HAROLD W. DARGEON, M.D., NEW YORK, N.Y.

Methods for the treatment of cancer other than conventional surgery and radiotherapy have been studied for many years. These methods have utilized various agents which produce an inhibitory or destructive action on the living cell. Broadly classified they consist of three varieties: cellular poisons, biological products and radioactive substances. The usual therapeutic results in this field of investigation have not been successful, but occasional suggestively encouraging effects—even of temporary nature—have maintained chemotherapy for the treatment of cancer as a point of therapeutic interest for many years.

During the last 10 years this interest has increased remarkably and there are now many investigations in the chemotherapeutic field proceeding in all parts of the world.

This report summarized the observations made on the Pediatric Service of Memorial Hospital for Cancer and Allied Diseases, in New York City. The total number of children studied was 60 and their ages varied from four months to 13 years. The diagnoses of the children treated were: leukemia 46, lymphosarcoma 3, neuroblastoma 4, endothelioma 1, Wilms tumor 1, rhabdomyosarcoma 1, and carcinoma of thyroid 4. Only those to whom no hope could be offered by conventional measures were treated by these agents. The agents used were: nitrogen mustards (4 members), urethane, aminopterin, radiophosphorus P^{32}, and radioiodine I^{131}. Because of the limited periods of observations, the effects of aminopterin and radioiodine therapy could not be completely evaluated.

The clinical results from the other agents were satisfactory in that no cures or satisfactory remissions were observed. Three questionable remissions were observed in our cases.

These studies, however, corroborate the many reports concerning the toxicity of all these agents for living cells particularly those of lymphomatous origin. Many related compounds are still to be produced and studied. One substance which has and is giving encouraging signs of therapeutic value is radio iodine I^{131}. More effective agents may, perhaps, be developed as the program progresses. Certain of these agents are being used in the adult with more satisfactory palliative effect.

4. HYPOCALCEMIC STATES

BY KATHARINE DODD, M.D., CINCINNATI, OHIO

(Published as Special Review, PEDIATRICS 2:737, 1948.)

5. LIPID DISTURBANCES

BY L. EMMETT HOLT, JR., M.D., NEW YORK, N.Y.

(See Summary)

6. DISTURBANCES IN CARBOHYDRATE METABOLISM

BY ALEXIS F. HARTMAN, M.D., ST. LOUIS, MO.

(See Summary)

7. DISTURBANCES IN PROTEIN NUTRITION

BY A. ASHLEY WEECH, M.D., CINCINNATI, OHIO

Physiologic consequences of inadequate protein in the diet were discussed. The relation of depleted serum proteins to edema was illustrated. Certain accessory phenomena consisting of a decline of basal metabolic rate, of a slowing in the heart beat, of a disinclination to engage in physical activity, of a diminution in the volume of the blood and of functional damage to the liver were pointed out. In discussing therapy, the need for conservatism in restoring fully adequate amounts of protein to the diets of starved individuals was stressed.

8. THE EXPERIMENTAL PRODUCTION OF PERIARTERITIS NODOSA, RHEUMATIC CARDITIS AND RHEUMATIC PNEUMONITIS

BY JOHN E. GREGORY, M.D., PHILADELPHIA, PA.

Rheumatic fever is a disease which attacks the connective tissue and blood vessels of the entire body. It causes 40% of all heart disease, and far more deaths in the first two decades of life than

the total of all the communicable diseases plus pneumonia. It produces 10 times as many deaths annually as does infantile paralysis.

The causes and the factors which influence the course of development of this important disease are not, as yet, clearly understood. The work reported in this paper has contributed to the growing belief among students of rheumatic fever that the disease results from allergic sensitization of the affected body tissues, probably to the same bacteria that cause scarlet fever and streptococcic sore throat.

The work reported was not designed to show the connection of bacteria with the disease, but rather to investigate the capacity of allergic sensitization to produce lesions in the tissues like those seen in rheumatic fever. To do this, rabbits were injected with large doses of horse serum, egg albumen or a mixture of the two substances. These substances, so injected, are known to produce a high degree of sensitization.

A suitable period of time was allowed to elapse after the injections and then the tissues of the animals were examined microscopically. In about half of the animals a disease process was observed in the blood vessels, heart and lungs that closely reproduced that seen in rheumatic involvement of these organs.

It is deduced from this evidence that a high state of sensitivity, or hypersensitivity, can produce the lesions of rheumatic fever. A great deal of evidence, piled up by earlier investigators, has connected the streptococcus with this disease but has also shown that there was no direct infection of the rheumatic tissues since there were no bacteria to be found in them. A synthesis of the evidence, therefore, suggests strongly that rheumatic fever is caused by hypersensitization of the affected body tissues to streptococci.

9. THE DIAGNOSIS AND PROGNOSIS OF RHEUMATIC FEVER

BY MAY G. WILSON, M.D., NEW YORK, N.Y.

(See Summary)

10. DIAGNOSIS AND PROGNOSIS OF CONGENITAL DISEASE OF THE HEART AND VESSELS

BY HELEN B. TAUSSIG, M.D., BALTIMORE, MD.

(See Summary)

11. CONGENITAL HEART AND VESSELS—CATHETERIZATION

BY ROY E. SEIBEL, M.D., BUFFALO, N.Y.

Venous catheterization has proved a valuable adjunct in the diagnosis of congenital heart disease.

The method consists of the passing of an opaque, woven silk, 9F catheter, 100 cm. long via the median basillic, axillary, subclavian veins and the superior vena cava into the right heart. The procedure is performed under local anesthesia and the catheter is passed under fluoroscopic guidance. Blood samples are withdrawn through the catheter from the pulmonary arteries, right ventricle, right auricle and superior vena cava. Pressures are recorded in these chambers by means of a Hamilton manometer attached to the catheter. Spot radiographs are taken of the catheter in each position.

In patent ductus arteriosus the significant finding is that of increased oxygenation of blood obtained from the pulmonary artery as compared with blood obtained from the right ventricle. The pressure in the pulmonary artery may or may not be elevated.

A left to right shunt as a result of an interventricular septal defect is indicated by finding

increased oxygenation of the right ventricular blood sample as compared to right auricular blood. The pressure in the right ventricle may or may not be elevated.

It has not been possible to pass the catheter through an interventricular septal defect because of the pressure difference between the left and right ventricle.

An interauricular septal defect is indicated by increased oxygenation of the right auricular blood as compared to vena cavæ blood. It is frequently possible to pass the catheter through the septal defect into the left auricle and into the pulmonary veins.

Three parts of the tetralogy of Fallot may be determined by venous catheterization. The interventricular septal defect is indicated as described above. The pulmonic stenosis is indicated by finding an elevated pressure in the right ventricle with a lower pressure in the pulmonary artery.

If the pulmonic stenosis is marked the catheter will pass into the aorta from the right ventricle indicating a dextro position of the aorta.

This method is of value in conjunction with the ordinary methods of examination in determining the type of congenital defect and in determining whether patients are suitable for surgical intervention.

12. MANAGEMENT OF HEART FAILURE IN INFANTS AND CHILDREN

BY MITCHELL RUBIN, M.D., BUFFALO, N.Y.

(See Summary)

13. THE MANAGEMENT OF NEPHROSIS

BY CHARLES A. JANEWAY, M.D., BOSTON, MASS.

Although the picture of nephrosis may develop in syphilis, amyloidosis, thrombosis of the renal veins, or after poisoning with certain drugs, the majority of cases are due to unknown causes. The management of a child with nephrosis can best be undertaken if one has an idea of the natural history of this condition in childhood. Whether one believes that there are two diseases—lipoid nephrosis and chronic glomerulonephritis with edema, or that these are two variants of the same basic process, everyone will admit that children with nephrosis who show persistent hypertension, hematuria, or nitrogen retention have a poorer prognosis than those in whom these signs are not observed. In the group showing these unfavorable signs, death due to renal or cardiac failure is apt to occur in a few years. In the group with so-called "pure" nephrosis, symptomatic recovery, with or without persistent albuminuria, occurs in a high proportion of cases who survive the period of several months to several years during which remissions and exacerbations of the edema continue.

In this group of patients (and to a much lesser extent in the first group) infection is the predominant cause of death. With the advent of sulfadiazine and penicillin, deaths due to bacteremia, peritonitis, and pneumonia have been markedly reduced in these children. Thus prompt treatment of any febrile infection with these drugs is indicated, and measures to reduce the incidence of infections are important. A second important cause of death is over-zealous therapy—reactions to intravenous injections, unwise tonsillectomies or other surgical procedures, or infections acquired during an unnecessarily prolonged period of hospitalization. Edema is the feature of nephrosis which incapacitates the child and disturbs his parents. There is no sure way to get rid of it, but with restriction of dietary sodium and paracentesis, it may be partially controlled. The use of serum albumin often gives transient relief, and the most satisfactory diureses occur unexpectedly after some acute infections.

Thus, nephrosis is a chronic disease with remissions and exacerbations, which will ultimately clear in many instances, if the physician protects his patient from the hazards of infection and too zealous treatment, and can keep the patient reasonably nourished and his parents moderately happy, while waiting for nature to effect a cure.

14. MANAGEMENT OF ORTHOPEDIC PROBLEMS IN PEDIATRICS (CONGENITAL DEFORMITIES)

BY WILLIAM T. GREEN, M.D., BOSTON, MASS.

Congenital abnormalities of the musculo-skeletal system are quite common, yet most of them, if properly treated at the right time, will cause little or no handicap. In many, the result attained depends upon the age at which treatment is started. Contractions become more firm as time elapses from birth and progressive distortion occurs with growth, so that even a few weeks makes a great deal of difference in the outcome. It is often easy to correct such abnormalities soon after birth; whereas, if the treatment is not instituted until some time later, it may be impossible to obtain complete correction. It is important that the pediatrician see that abnormalities of this type receive early attention. In some deformities, such as club feet, no diagnostic problem exists, but in others, such as congenital dislocation of the hip, early recognition may be difficult. Yet in both instances, treatment at an early stage is essential for the best result.

Other congenital abnormalities represent problems of long duration and may be of such consequence that more or less severe handicap results even after the maximal gain has been attained. Frequently the treatment and supervision must be continued throughout the period of growth. The therapy may need to be instituted immediately after birth and planned in successive stages at variable ages. Surgical procedures to correct deformities in children must observe at all times the factor of growth, and often procedures cannot be performed until a certain age is reached. It is satisfying for example to see a severe deformity of a lower extremity in a young child corrected by surgery, but, if in the doing an epiphysis is injured, the extremity may be several inches short when growth is completed; thus, though the immediate correction may appear to be excellent, the final result is most disturbing.

In those individuals whose deformities require prolonged arduous treatment, and particularly those who are to be permanently handicapped, the physician has many responsibilities other than seeing that the patient obtains the best possible physical result. The patient's morale must be kept at as high a level as possible. He must be directed in his activities, his education and training so that he may be socially and economically independent. He must be directed into a vocation which his handicap permits and his attributes allow.

(The treatment of specific types of congenital anomalies was discussed and illustrated.)

15. JUVENILE RHEUMATOID ARTHRITIS

BY L. MAXWELL LOCKIE, M.D., BUFFALO, N.Y.

(PEDIATRICS **2**:694, 1948.)

16. MANAGEMENT OF THE CHILD WITH CHRONIC ASTHMA

BY JEROME GLASER, M.D., ROCHESTER, N.Y.

The child with chronic asthma is one who has perennial attacks despite all efforts at alleviation. Every child should be carefully watched for the development of eczema, recurrent upper respiratory infections and pollinosis. These conditions, which are often the precursors of bronchial asthma, should be early and thoroughly treated although we are far from certain, as yet, whether such treatment, even if successful, will actually prevent the development of asthma.

Environmental control is exceedingly important. The allergic and therefore potentially asthmatic child, as well as the child with asthma, should be protected, regardless of the results of skin tests, from such common potential sensitizers as house dust, feathers and wool. He should not have pets with fur or feathers. In cold or damp weather the head and feet must be adequately protected. The bed room should be of an even temperature and not uncomfortably cool. All strong odors, particularly that of fresh paint, must be avoided.

The effect of change of climate in asthma is often very disappointing and in many instances

its supposedly beneficial effects have eventually been shown to be due to non-climatic factors as escape from environmental allergens or psychosomatic factors as disturbing situations in family life. Change of climate should never be advised until all local resources of study and treatment have been thoroughly exhausted. However, because many asthmatic children will even then be found to suffer exacerbations because of cold, dampness and sudden changes in temperature and perhaps other meteorologic factors, a change of climate must occasionally be tried.

Very often the physician is reluctant to administer routine prophylaxis against diphtheria, pertussis and tetanus in allergic children for fear of disagreeable reactions. These, however, occur less or no more frequently than in non-allergic children. If the physician wishes to be cautious, the injections may be given in smaller doses and more given so that the child will receive the theoretically adequate total dose.

Thorough consideration from the psychosomatic aspect must be given the child with chronic asthma. The asthmatic child may be over protected by the parents although the opposite situation or rejection may do as much harm. The child should be given a sense of complete security by the parents who should be thoroughly familiar with the symptomatic treatment of asthma. Because the child cannot do many things done by other children he may develop a sense of inferiority. Some hobby or accomplishment should be developed in which he can excel and truly feel himself the equal or superior of his non-asthmatic sibling or friend.

One of the worst errors which can be made by the parent or physician is to stop treatment of the child too soon because he has had a few weeks or months without attacks. The patient should not be discharged from treatment until he has had a minimum of at least one year of complete freedom from symptoms. Finally, the child should be aided in the selection of a career in which, if asthma persists or recurs, the earning of a living will not be completely impossible.

17. SPECIFIC DIAGNOSTIC METHODS IN THE VIRUS ENCEPHALOPATHIES

BY WALTER SCHLESINGER, M.D.

(Published as Special Review, PEDIATRICS 2:625, 1948.)

18. ELECTROENCEPHALOGRAPHY IN CHILD NEUROLOGY AND PSYCHIATRY

BY HERBERT JASPER, M.D., MONTREAL, CANADA

(To be published in PEDIATRICS as an Original Article)

19. SUBDURAL HEMATOMA

BY FRANC D. INGRAHAM, M.D., BOSTON, MASS.

(Advances in Pediatrics, Vol IV, 1948.)

20. THE RECOGNITION AND TREATMENT OF INCREASED INTRACRANIAL PRESSURE IN INFANCY AND CHILDHOOD

BY BARNES WOODHALL, M.D., DURHAM, N.C.

(PEDIATRICS 2:533, 1948.)

21. PEDIATRIC ECONOMICS

BY WARREN R. SISSON, M.D., BOSTON, MASS.

(Published in Academy Proceedings and Reports, PEDIATRICS 2:89, 1948.)

22. PSYCHOSOMATIC PEDIATRICS

BY FREDERICK H. ALLEN, M.D., PHILADELPHIA, PA.

(See Summary)

23. BGG VACCINATION AGAINST TUBERCULOSIS

BY KONRAD BIRKHAUG, M.D., ALBANY, N.Y.

The human species seems endowed with a high capacity for acquiring resistance to the tubercle bacillus. Experimental investigators and clinical experience have proved that a primary tuberculous infection confers a relatively significant resistance against a subsequent exogenous tuberculous infection. *A priori* it might be expected that artificial immunization in some form would meet with success. So far, research has yielded no such method which gives absolute protection. Of the two possible systems (a) the application of dead bacilli and (b) actual infection by living bacilli of strains that have no power to cause progressive disease, the former has given unpromising results. Immunization by living bacilli has been studied extensively in animals. So far, only the strain BCG (*Bacille Calmette-Guérin*) has produced significant immunity and at the same time so satisfied the requirements of safety in millions of people over more than 20 years as to be accepted for human vaccination on more than an experimental scale, and to a degree which would justify its general use in selected groups of tuberculin negative individuals exposed to a tuberculous environment.

Although there is still ample room for arguments about the degree and duration of immunity following BCG vaccination, as well as about methods of administering the vaccine, there seems to be complete agreement about the absolute harmlessness of BCG, that it produces tuberculin allergy in about 95% of the vaccinated persons within two months after vaccination, that the average duration of tuberculin allergy is five years, and that the protection produced by BCG against a virulent infection is almost as effective as that of the spontaneous infection, but notably without any risk of the disease from the vaccine itself. BCG has another advantage over most other vaccines in that it rarely produces either local or general discomfort. Although it fails to produce an absolute immunity against tuberculous disease, it is the most effective adjunct we possess today to the conventional tuberculosis control methods.

On the basis of results obtained in Europe and America, an appreciable reduction in the incidence of clinical tuberculosis may be anticipated in selected groups of people who are likely to develop tuberculosis because of unusual exposure, inferior resistance, or both, such as tuberculin negative doctors, medical students, nurses, hospital and laboratory personnel, inmates and employees of mental hospitals, prisons and other custodial institutions, children and certain adults considered to have inferior resistance and living in communities in which the tuberculosis mortality rate is unusually high and in particular children directly exposed to tuberculosis in the household anticipating the return of a "cured" sanatorium patient.

BCG vaccine will not be available for general distribution in the State of New York. Local full-time health departments are urged to evaluate the need for and the timeliness of a BCG program in their respective localities. For the present the vaccine will be distributed on request to local health departments, medical colleges and teaching hospitals, superintendents of public tuberculosis hospitals and directors of tuberculosis clinics, and to other institutions designated by the State Commissioner of Health.

The BCG vaccine is to be administered only to nonreactors to 0.0002 mg. PPD or 0.1 mg. OT and a chest X-ray is recommended before vaccination. A tuberculin control test should be performed two months after vaccination and if negative, revaccination is recommended. The entire vaccinated group should be observed for five to 10 years if possible with yearly tuberculin tests and chest X-ray and revaccination is recommended for those reverting to tuberculin-negative status.

Round Table Discussion

SYSTEMIC MYCOSES, COCCIDIOIDOMYCOSIS AND HISTOPLASMOSIS

J. C. PETERSON, M.D., *Chairman, Nashville, Tenn.*

INTRODUCTION

Chairman Peterson: In this discussion we will attempt to clarify concepts concerning the use of skin testing material in the diagnosis of these two fungus infections. We will also attempt to show the relationship of minimal mild infections to the more serious infections.

Until the recent past, most of us have considered fungus infections to play a very minor or unimportant role in the production of disease process in children. All of us have been more or less aware of the fact that thrush and certain dermatomycoses are commonplace in early infancy and childhood respectively but serious infections are so rare that they are of little significance. In general, fungus infections have seemed to play an unimportant role in the spectrum of disease processes; only occasional rare severe infections being recognized.

In recent years we have been forced to the realization that fungus infections—generalized fungus infections—are much more common than we had previously suspected and that many of these infections have remained unrecognized or they have masqueraded under false pretenses and have been classified as other diseases.

The study of coccidiomycosis in California first pointed out the fungus infections, which have been recognized only as a generalized serious infection, might also exist in a much more benign form and might have a course which is entirely asymptomatic or nearly asymptomatic. In most of the fungus infections the recognition of the severe form of infection has antedated the recognition of the benign forms of infection. That is true of both of the fungus infections which we will discuss today.

The discussion of coccidioidomycosis will be led by Dr. Russel Mapes of Beverly Hills, Calif., who—though he is a practicing pediatrician—has had extensive experience with coccidioidomycosis in his work in the Army.

Dr. Mapes: Coccidioidomycosis is an infection caused by the fungus Coccidioides immitis. It may occur as a mild, even inapparent infection, or in the more common pulmonary form which is self-limited and without sequalæ, or it may appear as the progressive disseminated disease known as coccidioidal granuloma. The history and background of this disease is interesting. The disseminated form of the disease was first described by Wernicke and Posados of Argentina in 1892. Rixford and Gilchrist described the first case in this country in 1896. The causative organism was at first thought to be a protozoan, and the name C. immitis was suggested by Dr. C. W. Stiles, then of the Bureau of Animal Industry. In 1900 however, Ophüls and Moffitt were able to demonstrate its fungus nature. Coccidioidal granuloma was the only clinically recognized form of this disease until 1936.

For many years it had been known that the incidence of erythema nodosum was much higher in the southern part of the San Joaquin Valley of California than in other parts of the country, and when associated with an "influenza-like" respiratory infection, the disease was variously referred to as San Joaquin Valley fever, valley fever, desert fever, or desert rheumatism. In 1936 and in 1937 Dickson & Gifford were able to demonstrate that C. immitis was the causative organism in this disease. All patients were thought to recover. Dickson suggested that the name coccidioidomycosis be employed for both forms of the disease, classifying as primary the acute initial infection, which was self-limited and non-fatal; and secondary the progressive disseminated disease, or classic coccidiodal granuloma.

Up to 1936 the total number of cases of coccidioidomycosis reported in California was only 450 of whom 224 had died. Yet Dickson found, by sending a questionnaire to 75 physicians practicing in the San Joaquin Valley, that a total of 354 patients with valley fever associated with erythema nodosum or erythema multiforme had been seen in the previous 18 months. All but one of these patients had recovered. In a similar period Dr. Charles E. Smith, Professor of Public Health and Preventive Medicine at Stanford University, investigating the disease in two counties of the

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southern part of the San Joaquin Valley saw 432 cases of acute coccidioidomycosis with erythema nodosum or multiforme. The illness in every case was associated with either a positive sputum culture or positive coccidioidin skin test.

Gifford and her associates found by testing 2718 school children in Kern County that 55% gave positive skin tests. The percentage varied from 17% for those of less than one year residence in the county to 77% for those living in the county 10 years or more. In one group of 143 positive reactors, only four gave a history of erythema nodosum, and in another group of 76 positive reactors only four gave a history of erythema nodosum.

Smith calculated on this basis that the 432 cases that he had seen must have represented some 8,000 to 10,000 infections. Thus a high incidence of coccidioidal infections of the population particularly of the inapparent, or sub-clinical type was demonstrated in this endemic area.

With the advent of war and the establishment of many military installations throughout the endemic southwest, the military implications of this disease were quickly appreciated by the Surgeon General's Office, Army Epidemiological Board, and the Army Air Forces Training Command. Therefore, control programs were instituted. Dr. Charles E. Smith of Stanford University was chosen as a consultant of the Surgeon General's Office to carry on an extensive survey on several airfields in the San Joaquin Valley of California. The results of this study have been published in the American Journal of Public Health, and have added much to our present concept of this disease.

The etiology of coccidioidomycosis as has been stated is C immitis, which is diphasic, and in the vegetative phase appears as a cotton-white colony and grows with ease on many media. It consists of long thin mycelia which segment and form chlamydospores. These chlamydospores are highly infective. This is the form that occurs in nature and was recovered from dust by Stewart and Myers in 1932.

In the parasitic phase, as seen in tissue sections, the organism is a spherule 5 to 80μ in diameter with a thick, double contoured refractile capsule. It enlarges as it matures, and its granular protoplasm breaks up into a large number of endospores, which are released when the spherule bursts. These released endospores then enlarge independently to form mature spherules, thus repeating the cycle.

So far as is known, it is limited chiefly to the Southwest in this country; the southern San Joaquin Valley of California, some in Riverside and San Bernardino counties of California; South and Central Arizona, West Texas; most of Texas along the Mexican border; the southern part of Nevada, and the southwestern part of Utah. It has its highest incidence during the summer during the dry season when it is dusty. All agree that the disease is acquired by the inhalation of dust contaminated with the chlamydospores, and that the only portal of entry is through the respiratory tract, with the possible exception that it might be acquired through skin abrasions. There is no recognized influence of age on susceptibility. The length of residence seems to be important. There is no difference as regards sex and race with respect to the number of positive skin reactions. Caucasian females have a higher incidence of erythema nodosum. Males have a higher incidence of dissemination of about four to seven times that of females. The dark-skinned races, particularly the Negro, Mexican and Filipino are more prone to the disseminated infection by about seven to 10 times that of the Caucasian race. Children are less prone to dissemination than are adults, except in the early years. Under four years of age the rate or dissemination is higher. From four to 15 dissemination occurs in about 8% of the cases reported in California.

As to the clinical types of the disease, the initial infection is always respiratory and is incurred by the inhalation of fungus in contaminated dust. It is focalized in the lung and in most instances subsides spontaneously and without sequelæ. It may be entirely asymptomatic; this is the usual type seen in the residents of an endemic area and can be shown only by a positive coccidioidin skin test. The most frequent clinical type is the "acute respiratory" infection which is self-limited and is mainfested predominately as a pneumonitis, a bronchitis, or a pleuritis. It is often indistinguishable, in fact, almost always indistinguishable from the common upper respiratory infections, except when accompanied by erythema nodosum and erythema multiforme; then, of course, it is much more easily recognized. Complete recovery is the rule, without sequelæ. However, a certain number of these cases—the exact percentage we do not know, perhaps somewhere around 10%—may show residual benign lesions, notably pulmonary cavitation and

pulmonary nodules, which are not accompanied by any constitutional symptoms, and are usually entirely asymptomatic and revealed only by X-ray.

In rare instances the initial infection does not subside but becomes progressive with either local pulmonary spread or with lymphatic and hematogenous spread to practically all organs, notably lymph nodes and meninges, bone, liver, spleen, etc. The clinical features of the disseminated disease depend on the organs involved. These cases run protracted courses and about 50% of them die. It should be emphasized that the disseminated phase occurs during the initial infection and represents a continuous progression of the disease.

The symptomatology of coccidioidomycosis is extremely variable as one might expect. The initial infection may be entirely asymptomatic. The acute primary infection may be protracted or it may be mild and its main symptoms are those of an acute respiratory infection or so called "influenza." Its chief characteristics are pain in the chest, cough, fever, arthralgia, night sweats, headache, anorexia, chills, etc. It is usually diagnosed as influenza or pneumonia, and in about 20% of the clinically diagnosed cases, erythema nodosum or erythema multiforme appears during the second or third week of the disease. The symptoms of the disseminated infection naturally depends upon the site to which the fungus is spread. Meningitis runs a chronic course with symptoms like tuberculous meningitis. The other forms can be compared to a disseminated tuberculous infection with high fever, prostration, loss of weight, anemia, and other signs of cachexia.

The physical findings in coccidioidomycosis in the acute phase, in the absence of erythema nodosum are of little diagnostic help. In spite of pleural pain, cough, and other evidence of systemic toxicity there is little to be found in the lungs on physical examination. The exception to this is when pleural effusion occurs to an extent that can be picked up; but the pneumonitis which occurs in coccidioidomycosis can rarely be heard on physical examination. The laboratory findings of the disease (except for the culture or animal inoculation test, which I will mention later) are of little specific value. Most of these cases run a mild leukocytosis from 12,000 to 15,000. In about 15% of the cases a mild (8 to 20%) eosinophilia occurs. They all have a rapid erythrocyte sedimentation rate. The most helpful laboratory finding is a serologic test for precipitins or complement fixation. It has been shown that early in the disease humoral antibodies occur in the blood serum and using coccidioidin as an antigen these can be shown to be present in the acute infection which are probably the greatest diagnostic help.

X-ray is of help, and the X-ray findings in coccidioidomycosis can be said to fall mainly into about four groupings: simply an adenitis, pneumonitis, the residual lesions of cavitation, or nodules. In X-ray films of the disseminated cases, of course, it may be entirely limited to the marked lymph gland enlargement, abscess formation, or miliary dissemination of tuberculosis by X-ray. X-ray films of bone lesions are destructive lesions that also resemble tuberculosis.

Now, as to the diagnosis of this disease, the absolute proof of the diagnosis, of course, depends upon recovery of the organism. In acute primary disease, recovery of the organism is difficult. Most of these patients have very little sputum. Most laboratories are not equipped to culture them, and it is a dangerous procedure; practically all people who work in laboratories acquire the disease. The diagnosis can be fairly well established with the following factors: One is a recent residence in an endemic area; a history of a respiratory infection, with or without erythema nodosum; positive coccidioidin skin test; serial X-ray examination of the chest, and one of the most important with the positive coccidioidin skin test is the serologic test of complement fixation which appears fairly early in the disease and is diagnostic. A word should be said about coccidioidin skin test because it has the same significance and the same limitations as does the tuberculin test. A person with a positive skin test does not necessarily have the disease, but the test shows that he has been infected, and at some time had the disease. Coccidioidin is usually used in 1 to 100 dilution, or 1 to 1000, and is given 0.1 cc. intradermally exactly as the tuberculin test, and is read exactly as you would a tuberculin test in 48 hours —a positive test has the same requirements as that of the tuberculin test. Even in the endemic areas it is difficult many times to positively establish the diagnosis of this disease and it is most frequently confused with the common respiratory infections, viral pneumonia, or so called pneumonias. There is no specific treatment in the acute primary disease. The object is to afford the patient with conditions for focalizing his infection with adequate rest and general measures. They should be confined to bed until their chest is clear by X-ray film, and their sedimentation rate

has returned to normal. The average duration of this hospitalization in most of these cases is about one month. Some of them clear earlier than that. In the disseminated infection there is no known effective treatment. Many things have been tried, and all have been without effect.

Dr. S. R. Kaliski, San Antonio: Are there any theories as to why Negroes and Mexicans are particularly susceptible to disseminated granulomas?

Dr. Mapes: The only explanation is a racial characteristic and that they do not focalize or handle the infection as well as the Caucasian race, as experienced, let us say in tuberculosis.

Dr. P. C. Crone, Cleveland: What will be the outcome of these large pulmonary cavities?

Dr. Mapes: That is a debatable question, and we do not have a final answer. One should treat them conservatively, particularly the asymptomatic ones, because a majority of them will close in a period of two to three years, and we have seen a fair number that have closed spontaneously. Given a patient with a large pulmonary cavity that is having recurrent hemoptysis, lobectomy should be seriously considered. The use of artificial pneumothorax for coccidioidal cavitation is not universally accepted.

Dr. C. F. Wagner, Cincinnati: What about the incidence in children? Most of this work was done on adults, wasn't it?

Dr. Mapes: The incidence of sub-clinical or inapparent coccidioidomycosis in children in endemic areas is fairly high, as shown by the positive coccidioidin skin test. Positive skin tests are uncommon under two years of age. The only statistical data on the disseminated cases are those of the California Public Health Department. In the series of 450 cases, of which 224 died, 8% of these were under 15 years of age, the majority of these being under four years of age.

Question: Did you say one attack was immunizing?

Answer: It is believed that one attack is immunizing and that exogenous reinfection does not occur as it does in tuberculosis.

Question: Where can coccidioidin be obtained?

Answer: Dr. Charles E. Smith, Stanford Medical School, San Francisco, Calif.

Chairman Peterson: Dr. Michael L. Furcolow will begin the discussion on histoplasmosis. He is a member of the United States Public Health Service attached to the field section on tuberculosis and has a special interest in the problems of histoplasmosis with which he has been working for the past three years.

Definition

Dr. Furcolow: Histoplasmosis is a subacute to chronic infection caused by the fungus *Histoplasma capsulatum*. It is characterized by a primary, usually benign and widely prevalent form; and a secondary, disseminated, relatively rare and often fatal form. In these characteristics the disease resembles tuberculosis and coccidioidomycosis. This concept of the disease is based on the epidemiologic observations to be discussed presently, and is at variance with the opinion one would derive from a study of the reported cases up to 1948. Up until this year, the great majority of the reported cases illustrated the disseminated, systemic form of the disease and gave credence to the belief that the prognosis was just about hopeless, since almost all these patients died. A few cases of localized granulomatous lesions with recovery had been reported up to 1948. Reports of recovery from even the disseminated disease have been increasing, however, and histoplasmosis is now considered to be a relatively benign disease.

Background

The disease was first found in 1905 by Darling in the Panama Canal Zone. He reported a fatal case which pathologically resembled kala-azar. In 1907 he found several more cases. He thought the causative agent which he saw in the tissues was a protozoan which he named H. capsulatum. Six years later Roche-Lima looked at Darling's pathologic sections and thought that the organism was a fungus. The name of the organism was not changed, however. It was 20 years later that the first case was reported in the United States by Riley and Watson in Minnesota. In 1932 De Monbreun working in Tennessee, first isolated the etiologic agent in culture from a human case.

Approximately 100 cases have now been reported in the literature. As has been mentioned, these cases were almost all of the disseminated form, most of them fatal. The recent literature contains reports of definite recovery in two cases and questionable recovery in three others of disseminated disease, as well as reports of several cases in which the infection was localized and superficial.

In many respects the disease resembles coccidioidomycosis. Both were first thought to be protozan infections. Both were originally regarded as almost universally fatal; whereas, later research revealed that fatalities were rare and mild infection common. Both are sharply localized geographically—coccidioidomycosis to the Southwest and histoplasmosis to the East Central part of the United States.

Etiologic Agent

Histoplasmosis is caused by a fungus, which, like the fungus causing coccidioidomycosis, has two phases in its life cycle: The yeastlike or parasitic phase and the mycelial or saprophytic phase. The organism has never been isolated from nature. Because its life cycle has not been completed, it is classed with the so-called fungi imperfecti.

The yeastlike phase which is found in the tissues of the warm blooded host grows on artificial media at 37°C. but reverts to the mycelial type of growth at room temperature. The yeastlike phase, as it occurs in animal or human tissue, is a small oval organism about 1 to 5μ in diameter surround by a clear capsule. The central body stains well with hematoxylin and eosin, Giemsa or Gram stain. The organism is an intracellular parasite of the reticuloendothelial system.

The appearance of the organism in culture depends on whether it is in the yeastlike phase or the mycelial phase. In either phase, the organisms grow best on a medium containing blood, such as brain-heart infusion with blood. The yeastlike phase grows best at 37°C. and rather slowly. Growth is not evident until a week or 10 days has elapsed. On blood media at 37°C. the colonies are moist, soft and gray-white and somewhat resemble a staphylococcus colony. There is nothing characteristic in the gross or microscopic appearance of the organism in the yeastlike phase.

The mycelial phase grows best at room temperature (approximately 25°C.). It is characterized by a white, fluffy, mycelial growth on which the characteristic chlamydospores are found. Primary isolation of this phase is best accomplished also on media containing blood. Three or four weeks often elapse before colonies are visible. The mycelial phase will also grow on Sabouraud's or potato dextrose media. The appearance of the young colony is not characteristic, being white and fluffy. Older colonies show a characteristic brownish coloration of the media beneath the colony best seen from the reverse side. For final identification it is necessary to subculture to Sabouraud's or potato dextrose media as the characteristic chlamydospores will not appear on media containing blood. After a week or 10 days' growth, the characteristic chlamydospores appear on the mycelia. These vary from round to pyriform structures 8 to 15μ in diameter with thick walls. These chlamydospores are distinguished by the development of numerous tuberculate projections through the walls. The tuberculate chlamydospores serve to differentiate this organism from other pathogenic fungi.

There are a number of special points to be made concerning laboratory identification. Among these are:

1. Since the fungus grows slowly, it may well be missed if cultures are discarded after a week or 10 days as is customary in many bacteriologic laboratories.

2. Cultures which are incubated at 37°C. do not grow in the mycelial phase but in the yeastlike phase, hence colonies might be easily overlooked by a technician looking only for mycelial growth as the indicator of the presence of a fungus.

3. Certain saprophytic fungi which are extremely common air contaminants are very troublesome in obscuring the pathogenic fungi. These saprophytes grow rapidly and in several days may overgrow the culture plates and thus obscure the presence of the slower growing pathogens. This is especially troublesome in culturing air, water, or soil.

4. The absence of the typical tuberculate chlamydospores on young cultures requires that the colony be observed for a sufficient time for the characteristic spores to appear.

5. Although the ideal animal for isolation is yet to be found, small animals such as mice or hamsters seem more useful than guinea pigs since mice occasionally die of the infection, whereas guinea pigs usually do not even if infected by large inocula. Animals showing no gross pathology at autopsy may yet yield positive cultures and the characteristic histologic appearance of parasitized tissue.

6. Contaminating bacteria, formerly quite a problem in the cultures, have been largely eliminated by the addition of 20 units of penicillin and 40 units of streptomycin /cc. of culture media which is employed in the isolation of the fungus.

Pathogenesis and Pathology

The organism is a parasite of the reticuloendothelial system and hence is found in places where the cells of this system are most numerous; namely, the lungs, liver, spleen, lymph nodes, adrenal glands and bone marrow. Perhaps the general pathology is best divided into lesions of skin and mucous membranes and lesions of the internal organs. Ulcerative lesions may involve the skin and the mucous membranes of the nose, mouth and intestinal tract. Lesions in the internal organs occur in the lungs, liver, spleen, lymph nodes and adrenal glands. In most of the fatal cases the organism is disseminated throughout the body and can be isolated in culture from almost every organ. The pathologic response is a granulomatous reaction which is characterized by epithelioid and giant cells. This pathologic reaction is similar to that seen in tuberculosis or coccidioidomycosis. Pathologically, the diagnosis is made by the finding of the organism in histologic sections of infected tissues. While this may sound easy, it is obvious from the scarcity of reported cases, that it is not. The principal reason for the infrequency of pathologic diagnosis is the small size of the infecting organism which is about half the size of a red blood cell. In addition, the organisms may be relatively rare in the tissues and hence found only with considerable difficulty. It is desirable to employ the oil immersion lens for final identification of the organisms as they may be missed by the high dry lens. Since the pathologic response to this infection consists of a granuloma, the histologic components of which include epithelial cells, giant cells, and often necrosis, it is easily understood why this disease has been frequently confused, pathologically, with tuberculosis.

Epidemiology

This presentation will combine the work of all the various groups which have been working on the problem so as to give as complete a picture as possible of the epidemiology of this disease. This discussion is divided into that of the benign form, that is, the form characterized by histoplasmin sensitivity, and that of the disseminated form. The benign form will be discussed first.

As has been illustrated by Palmer, and also by Christie and Peterson, the geographic distribution of the disease, as indicated by histoplasmin sensitivity, is quite interesting. It is limited largely to the East Central United States from Eastern Kansas to Middle Ohio and from Southern Iowa to Middle Louisiana. In this area about 70% of young adults have been found to be histoplasmin positive. As one moves away from this central area in any direction, with the possible exception of Virginia, the rate falls. It is interesting to note that this area of high histoplasmin sensitivity is also the area where large numbers of men had been noted by Selective Service to have calcified lesions in their chest X-rays.

This problem of the occurrence of calcified chest lesions in the X-rays of tuberculin negative people in this general area had been commented upon a number of times, beginning in Tennessee in 1938. As a result of these findings, the validity of the tuberculin test as an epidemiologic indicator of tuberculous infection was brought into question. This in turn stimulated extensive studies on the significance and usefulness of the tuberculin test. The outcome of these studies was that tuberculin employed in relatively low doses (.0001 mg. of PPD) is a specific testing material for indicating past or present tuberculous infection. This dose, only slightly stronger than the first testing strength of either OT or PPD, appeared to be satisfactory for eliciting reactions in well over 95% of proved cases of tuberculosis, at the same time producing reactions in very few persons who appear not to be infected on the basis of history and careful work-up. On the other hand, if larger doses were used, such as second strength or larger, a number of nonspecific reactions were encountered and the specific reactions could not be distinguished from the nonspecific.

Support for the specificity of tuberculin only in low doses is found in studies of the persistence of the tuberculin reaction in persons once positive. Dahlstrom in 1940 showed that less than 3% of reactions to the first test dose reverted to negative; whereas, 60% of those positive to the second strength test reverted to negative. These studies were based on an average of nine years of follow-up and retesting.

On the basis of such observations on the specificity and persistence of the tuberculin reaction, it seemed necessary to conclude that tuberculosis was not the cause of the calcified lung lesions in tuberculin negative persons. Smith first suggested that histoplasmosis might be the cause of these lesions; this suggestion was pursued by Christie and Peterson while working in Tennessee and

by Palmer who attacked the problem on a nation wide scale. Most pulmonary calcifications were found to be associated with either a positive histoplasmin or a positive tuberculin test. In the East Central area of the United States, more cases were associated with a positive histoplasmin than with a positive tuberculin test. In Tennessee 4% of the calcified lesions occurred among tuberculin positive persons and 66% among histoplasmin positive persons. Palmer's figures for various states show considerable variation, but in general about 12% of student nurses with calcifications were tuberculin positive while 67% were histoplasmin positive.

Specificity of the Histoplasmin Reaction

Obviously the proof of the existence of mild primary histoplasmosis rests on the specificity of the histoplasmin reaction. The proof of the specificity of the skin test rests on the following:

1. Skin sensitivity to histoplasmin develops in animals inoculated with H. capsulatum.

2. Although it has been reported that in experimentally infected animals skin tested with various fungus antigens, varying degrees of cross reactions among the different fungus antigens are found; more recent work has shown that very few cross reactions occur if careful attention is paid to the dosage of antigen used in the skin test. Although the matter is not yet settled, it appears that most of the cross reactions reported can be explained by the use of doses of the skin testing antigens which are too large. This phenomenon of nonspecific reactions to large doses of skin test material is analogous to that encountered in the work with tuberculin as already discussed.

3. Histoplasmin skin tests in proved cases of histoplasmosis have been positive in most cases that were not critically ill at the time of testing. Seven of our 10 cases were positive to histoplasmin. Those that were negative were tested near death. Three additional unreported cases were also positive. Similar results are to be found in the literature; however, of the cases reported as having been tested, a greater proportion were near death at the time of testing than among our 10 cases. It is advisable to repeat the tests several times in suspected cases, since several of our cases were negative on first test but repeatedly positive on later tests.

4. Tests with various fungus antigens on proved human cases have shown only an occasional cross reaction with blastomycin. These few cross reactions are eliminated by serial dilution of histoplasmin and blastomycin. The histoplasmin reactions were shown to persist at greater dilutions than were the blastomycin reactions.

5. That histoplasmosis need not be always fatal is shown by the follow-up of our 12 cases, five of whom are dead, three still ill and four recovered. Another recovered proved case with positive skin and complement fixation tests has been found by the University of Cincinnati Department of Pediatrics.

6. Almost all tuberculin negative persons with pulmonary calcification will react to histoplasmin. This is true even in areas where the general histoplasmin rate is relatively low.

7. Active lung lesions among school children in Kansas City are much more likely to be associated with a positive histoplasmin than a positive tuberculin reaction. A follow-up of these lesions over a period of three or more years shows the slow development of calcification without change in the skin tests.

8. A complement fixation test has been developed which appears to be specific for histoplasmosis. All but one of our 12 proved cases have shown the presence of complement-fixing antibodies, 10 showing complete fixation otherwise referred to as a positive test result. In addition patients with active lung lesions and a histoplasmin skin test have shown positive complement fixation tests. Such positive tests have not been found among persons with healed chest lesions or those known to have tuberculosis or among those with negative histoplasmin skin tests.

A review of the literature makes it evident that certain epidemiologic facts are becoming clear regarding this disease both in the mild or benign form and the disseminated form. The epidemiology of the benign form will be considered first:

1. Importance of the infection. It has been estimated that in children, histoplasmosis (as indicated by a positive histoplasmin skin test) is almost 10 times as prevalent as tuberculosis (as indicated by a positive tuberculin test) in the East Central United States. Based on prevalence rates at various ages and population figures for the area of high histoplasmin sensitivity it appears that approximately 260,000 children under 15 years of age would react to tuberculin compared to 2,300,000 to histoplasmin.

2. Prevalence. The infection is very prevalent in the high endemic areas since about 80% of the population are infected by the age of 15 in Tennessee and Virginia. This same proportion of the population in Missouri is infected by the age of 22.

3. Age. Beginning at about 2½ years of age, there is a fairly constant increase in reaction rates with age.

4. Sex. Males appear to show slightly more positive reactors than females at any age group.

5. Race. Negroes are slightly less sensitive than whites of the same age.

6. Family. There is a slightly greater tendency for possible reactors to fall into families with other positive reactors than into families with negative reactors.

7. Histoplasmin sensitivity does not parallel tuberculin sensitivity as only about 18% of persons aged 20 are positive to tuberculin in Missouri as compared to 80% to histoplasmin.

8. Histoplasmin sensitivity differs with climate. In Tennessee, of persons living in a damp area 87% reacted, while of persons from a dry area only 67% reacted.

9. Contiguous areas differ greatly in sensitivity. Tennessee, Iowa, Kansas, Ohio, Louisiana and Illinois have been shown to differ markedly in percentage of reactors in different parts of the state.

In contrast to the epidemiologic findings reported above for the benign form of histoplasmosis the summary below was obtained from a review of reported cases of disseminated disease.

1. Age. There seems to be a slightly greater incidence in younger persons than expected as 25% of the cases occurred in patients under 10 years of age.

2. Sex. The incidence of this disease showed no sex difference in infancy or childhood, but adult males were much more commonly affected than females.

3. Predisposing causes. The disease appears to attack the very young or the very old or those ill with other diseases. Thus six cases of coexisting tuberculosis and two of coexisting Hodgkin's disease have been reported.

4. Animal reservoir. The disease has been proved in at least seven dogs, 10 rats and a mouse.

5. Household occurrence. Only once instance has been reported of two cases in the same family. A dog living in the home of a person with histoplasmosis has been shown to also have the infection. Histoplasmosis has been proved in a mouse obtained on the premises where an infected dog had lived.

Chairman Peterson: In the continuation of the discussion we will take up the symptoms which occur with hostoplasmosis; the objective clinical manifestations, in some detail; consider the question of prognosis; and finally summarize the whole briefly.

As most of you are aware, histoplasmosis in the fatal form has been reported in this country more than from any other place in the world and there have been today about 100 individuals who have had biologically proven histoplasmosis. This does not mean that these individuals represent all of the cases of histoplasmosis which have occurred. For example, at Vanderbilt University Hospital we have now proven biologically the existence of histoplasmosis to the extent of 20 cases, and of these cases only five have been reported in literature. There are in many hospitals in the Middle West examples of histoplasmosis either recognized or unrecognized which have not been reported. In recent years as cases have become more commonplace many single case studies are filed without their being reported. Dr. Furcolow pointed out that this disease has been known since 1905. The great majority of recognized cases have occurred only in recent years. This is not to be interpreted as meaning that this disease has suddenly become more prevalent. This increase in recognition is due to the fact that people are becoming interested in the infection and with increasing knowledge and careful study more cases are being found. Pathologists are also examining tissues specifically for the presence of H. capsulatum. This increased recognition of fatal cases has given us a wider understanding of the general pathology of the infection even in cases which might not be fulminating.

The symptoms and clinical manifestations of the infection in infants in our case material is beginning to provide a clinical picture which makes recognition of the disease fairly simple. The patients are brought to the hospital after having been ill for several weeks with the complaint that they are not well, that they are losing weight and are showing increasing irritability. Most of them are pale and many of them have shown a certain amount of inanition. In some of them the family have noticed prior to their admission enlargement of the abdomen due to enlargement of the liver and spleen. In some of them there has been progressive, nonproductive cough. It is not uncommon to find ulcerative lesions of the oropharynx. These have been more commonplace in adults

than they have in children. Secondary to these lesions in the mouth and throat some individuals have had moderate to marked enlargement of the cervical lymph nodes. Ulcerative lesions of the gastro-intestinal tract have been encountered in a number of patients and in some of them have been responsible for the chief symptoms and to the circumstances which led to the death of the patient. These lesions are more common in the ileum and jejunum and lead to the production of vague abdominal pains with watery diarrhea and marked loss of weight. Curtis has also reported the finding of chancre-like genital lesions.

Physical examination may reveal the presence of pulmonary lesions. These may be either localized or diffuse bronchopneumonic processes but at times the involvement of the mediastinal lymph nodes may also produce obstructive lesions suggestive of the presence of a foreign body or of pulmonary and mediastinal tumors. In some far advanced cases the pulmonary findings may be similar to those encountered in miliary tuberculosis; there may be marked decrease in the vital capacity; and on X-ray examination of the lungs there may be diffuse generalized infiltration with small discrete lesions.

The pallor and anemia present in these patients often suggests the possibility of a primary blood dyscrasia. The anemia is usually moderate to profound with a marked degree of hypochromia and an associated granulocytopenia. These findings together with the marked enlargement of the spleen and liver and the occasional enlargement of regional lymph nodes are often interpreted as suggesting leukemia in the aleukemic phase. The platelets are not generally decreased in histoplasmosis while they commonly are in leukemia. The examination of the bone marrow, however, usually enables us to rule out the possibility of the patient's having leukemia. Other usual laboratory observations are not often significantly altered.

The diagnosis of histoplasmosis can be made by cultural means when the disease is in the progressive disseminated form. Positive cultures may be obtained from the blood in a high percentage of these cases and in a still higher percentage from cultures of the bone marrow. They may also be obtained from culturing materials aspirated from the liver, the spleen and lymph nodes. These cultures are best performed by using poured plates with fairly large amounts of good infusion agar enriched with 10% plasma or blood. The plates should be carefully sealed to prevent their drying out and be incubated at room temperature for at least five weeks before they are discarded. Where the material to be cultured may be contaminated with other organisms it should be treated with penicillin and streptomycin and incubated at 37° for a few hours to inhibit the bacterial contaminants before being incorporated in poured plates. The organism appears in culture plates first as a cottony white aerial growth, the underside of which has a brownish yellow color. After the cultures have been grown for a week or so the typical chlamydospores, which identify the cultures, appear. First is the aerial growth of mycelium, a white fluffy growth without gross distinguishing features; second is the microscopic view of the mycelium showing the septate strands with fat globules and the typical conidia which help to identify the cultures. Also shown in this slide, under low power, are the chlamydospores. In the next slide is shown a chlamydospore under high magnification and showing the tuberculate projections which give it the appearance of a war club. It is this structure which finally identifies the culture of H. capsulatum. In the next slide are shown the free growing yeast cells with their highly refractile capsules. These yeast cells when seen in the large mononuclear phagocytes in the infected individual also serve to establish the diagnosis of histoplasmosis with relative certainty.

The diagnosis of the infection by serologic means presents the difficulties indicated by Dr. Furcolow. In general one can say that properly applied and interpreted skin tests when positive serve to establish the fact that an individual has been infected with H. capsulatum, but like the tuberculin test they do not identify the type or state of the infection; also that they may be negative in patients with overwhelming infections. It is possible that refinements of the intradermal sensitivity tests, using fractions of the organism may help to differentiate the state of the infection but this is only a theoretical possibility.

The complement fixation tests which Dr. Furcolow and his group have introduced seem to offer a more probable method of distinguishing active and latent or past infections with H. capsulatum. This slide, from Dr. Furcolow's study, shows that he succeeded in getting strongly positive complement fixation tests in seven of nine cases with culturally proven active histoplasmosis, a higher percent of positive tests than he could obtain with skin tests. The child who did not react had had a brief course and died within a week, presumably a person with poor inhibition of the infection

and little or no capacity to respond. The other patient showed a weak positive reaction and was also a fulminating case. The second slide on complement fixation shows the reactions in those individuals with positive skin tests but without the cultural confirmation of their infection. Those with recent change from negative to positive skin sensitivity seem more likely to show positive complement fixation while those with latent or healed infections are generally negative.

In addition to the groups of patients with disseminated progressive histoplasmosis and the group with benign inapparent lesions, there is also a group, similar to the intermediate group in coccidioidomycosis, a group of patients with symptoms and findings from the infection but who are able to suppress the progression of the infection. From our experience this group is very small if one includes only those patients who have frank active clinical manifestations. If, however, one includes those individuals who have pulmonary lesions demonstrable by roentgenography, asymptomatic or nearly so in themselves but which go on to develop pulmonary calcification, one would include about half of the individuals who show dermal sensitivity to histoplasmin. This percentage of infections, histoplasmin sensitive individuals, showing demonstrable pulmonary scars, calcifications, is twice as high in histoplasmosis as in coccidioidomycosis, 60 to 75% as contrasted with the 25 to 30% of coccidioidin positive individuals showing calcifications and is more than three times as high as the percent of primary tuberculosis cases, tuberculin positive individuals, who show pulmonary calcifications.

Next we have a number of slides of roentgenograms showing the lesions which we have come to think of as being suggestive, if not specific for histoplasmosis. The first film is a typical tubercle with the small discrete calcified pulmonary focus, the fibrotic lymphatic tract extending back to the hilus and a solitary calcified hilar lymph node. This child had a positive tuberculin reaction and was negative to histoplasmin. The second roentgenogram is from a child who was sensitive to histoplasmin but negative to tuberculin. Here there is again a solitary discrete calcified pulmonary focus just above the diaphragm and a solitary calcified regional lymph node. Morphologically these two lesions are quite indistinguishable.

You may ask if the second child might not have had a tuberculous infection and subsequently lost his tuberculin allergy. The studies of Dr. Hardy show, however, that individuals with demonstrable pulmonary lesions do not lose their tuberculin sensitivity over a period of less than 10 years as an average and this child was only nine years old. It is highly improbable that he could have acquired and lost tuberculin sensitivity from such a lesion in the period of time which could have elapsed. We believe that this represents a minimal infection with H. capsulatum which has healed to the point of calcification but which has left him with histoplasmin sensitivity. This is not, however, the lesion which we believe to be most characteristic of histoplasmosis. In the next roentgenograms are shown individuals with multiple calcifications, the first shows a half dozen small discrete calcifications scattered throughout both lung fields and the second shows an individual with many "miliary" calcifications. These we believe are due, almost invariably in patients from middle Mississippi basin, to histoplasmosis. The next roentgenograms show individuals with massive calcifications of the hilar lymph nodes, lesions often 2 to 3 cm. in diameter. These are commonly composed of clusters of smaller calcifications, a mulberry lesion. These findings were independently observed by our group at Vanderbilt University and by Dr. Furcolow and his associates working at the University of Kansas and elsewhere.

In older individuals some calcified lesions may be absorbed and the next films taken at an interval of several years show the disappearance of some of the many calcified nodules present. This probably explains the fact that teen-aged children have more pulmonary calcifications than do the adults in the same community.

The final roentgenogram shows the chest of an adult with an extensive pulmonary infiltration and associated cavitation, morphologically identical with tuberculosis of the lung. He had no tubercle bacilli in his sputum and his tuberculin reaction was negative. His sputum did contain the yeast cells of H. capsulatum and he was exquisitively sensitive to histoplasmin. Before rest treatment was instituted he was losing weight and was going downhill. Now he is improving and it seems probable that he may be able to go on and heal his lesions.

We have also approached the development of calcifications in minimal pulmonary infections in our well baby clinic. We are following these infants with serial histoplasmin tests and when one of these infants changes from a negative reaction to positive we immediately get chest roentgenograms. In a number of these infants we have been surprised to find pulmonary infiltrations

which were entirely asymptomatic and which were not to any appreciable degree interfering with the growth and development of the child. We have also found more extensive and serious pulmonary lesions which were producing some symptoms though relatively minimal in relation to the degree of infiltration. We have not followed these long enough to see them become calcified on healing but we expect that they will in many instances.

We have attempted to prove culturally that these infections were due to H. capsulatum, but our attempts have borne very little fruit. We have tried to isolate the fungus from sputum and from gastric washings with no success and in these minimal infections it has not been possible to secure positive blood or bone marrow cultures.

We believe the failure to obtain positive sputum and gastric washing cultures arises from the fact that the yeast cells of H. capsulatum are primarily intracellular parasites and that they are only very rarely in the sputum, as in the patient cited above who had pulmonary destruction and bronchial ulcerations.

In several patients with disseminated progressive terminal histoplasmosis we have been unable to grow the organisms from sputum. This would, of course, make it highly improbable that one could secure positive cultures by this means in minimal cases. It has been fairly simple, as a rule, to cultivate the organism where there are ulcerative lesions though one can get more uniformly positive cultures in such instances from biopsy of the ulcer margin.

The outlook for improvement in patients with the disseminated forms of infection which has progressed to the point of producing clinical symptoms and for recovery in these adult patients who have chronic ulcerative lesions of the oropharynx and gastrointestinal tract is very poor. Most of these cases progress rapidly on to a fatal termination or persist as low grade chronic granulomatous lesions. This course is not invariable. Dr. R. Blumberg has recently told us of a case he is reporting where the child had marked anemia due to histoplasmosis proven by cultures from bone marrow, blood, spleen and liver who improved slowly and who is now well more than a year after the acute illness.

No therapeutic measures have been of any benefit in progressive histoplasmosis. All the dyes, metallic salts, sulfonamides and antibiotics known to be useful in chemotherapy have been unsuccessfully utilized. None so far have shown real promise of being effective.

In summary, we believe that H. capsulatum can produce a wide spectrum of local and generalized disease. That it is only in the rare and exceptional case that progressive infection occurs even where the primary infection may have been quite widely disseminated. Some of the lesions produced by histoplasmosis are morphologically identical with those of tuberculosis and in the past confusion has resulted from this similarity. The geographic distribution of this infection appears to be quite sharply demarcated with the greatest prevalence in the basin area at the confluence of the great mid-continental rivers.

Discussion

Dr. W. E. Keiter, Kinston, N.C.: Has anyone ever found organisms in a calcified lesion?

Chairman Peterson: We have not found the organism in calcified lesions. It is probable that we will not find them there. Where the lesion is calcified, the organism will have died out or will have become so changed it would be impossible to recognize or cultivate it.

Dr. W. A. McGee, Richmond: Have any patients had meningeal involvement?

Chairman Peterson: To date none have had meningitis, clinically recognizable, but one of our cases showed some meningeal infiltration associated with organisms within local phagocytes at postmortem examination, though he had had two normal spinal fluid examinations shortly before death.

Dr. R. Craig, Kokomo, Ind.: What about the incidence of secondary infection with histoplasmosis? Is it increased?

Chairman Peterson: In some instances it's almost impossible clinically to distinguish the progressive pulmonary form from pneumonia; whether it predisposes to the development of pneumonia, I could not say definitely but we have not observed such instances. What would you think about that, Dr. Furcolow?

Dr. Furcolow: Our cases were mild and we couldn't tell going back in to the histories. We went back into school and checked all our history illness records and we couldn't find any way of separating people who had changed and developed positive histoplasmin reactions.

Dr. M. C. Carlisle, Waco, Tex.: What percentage of positive skin tests were found in residents of Texas?

Chairman Peterson: Our studies showed about 26% positive reactions in Texas residents and Dr. Palmer's studies showed about 23% positive reactions. We do not, of course, know how many of these individuals have been out of the State of Texas and who might possibly have picked up their infection elsewhere. Those data are based on the primary residence of the individual tested.

Dr. Waring found in South Carolina, for example, only eight positive tests in some 300 individuals and five of those had been outside of the state either on prolonged visits or had come there from endemic areas on the western side of the Appalachians. It is not possible from our studies or those of the United States Public Health Service to say how prevalent histoplasmin sensitivity is in young infants in Texas. The studies shown on the map were based on observations on student nurses, age about 20, and 23% gave positive reactions in this area. In Tennessee, Kansas and Missouri, as you move away from the area of most intense prevalence you find the prevalence falling off. For example, the prevalence in Kansas City, which is high—above 65%—falls off coming as one goes west to about 7% at the Colorado border. In other words, in western Kansas it's only one-tenth of what it is in eastern Kansas. I suspect that as you move south and west in Texas the prevalence would fall. It would be higher here and drop off further west.

Dr. Carlisle: How long is histoplasmin stable after dilution?

Chairman Peterson: It's probably stable for about four or five months. We've tested material that has been kept in the ice box for a year diluted 1:100 without finding any appreciable loss of strength. Certainly material three or four months of age that has been kept in the ice box will not have lost potency enough to affect tests.

Dr. McGee: Is that true of the tuberculin and coccidioidin?

Dr. Mapes: Dr. Smythe carried a vial of coccidioidin around in his bag unrefrigerated for four years and it was still potent. I don't think it's recommended to keep it that long. We don't keep it over a week or two.

Dr. Furcolow: I don't think it makes any difference whether you use PPD or OT. OT may be a little better in that it will keep longer and keep a little better. The state health departments in some of the states are sending out tuberculin dilutions once a month so they figure that they will keep that long. We haven't been using it after a week but we are being extra careful about the tests.

Dr. Craig: What is the source of this infection?

Dr. Furcolow: The source of H. capsulatum in nature is not known. The epidemiologic data suggest that it is to be found free in nature but isolation has not been accomplished. Dr. Emmons studied a great many animals in Virginia in relationship to cases which he and others reported. I have already mentioned the finding of histoplasmosis in some of those animals, in rats and mice. It has been reported a number of times in dogs. Animals, from the experience to date, are probably not an important source of the infection. When you correlate positive skin tests in the population with the presence or absence of dogs and cats, cows and horses in the environment there is no correlation between the findings.

Dr. H. F. Downing, Cincinnati: Did you ever have an individual who had a benign infection and then got a reinfection? What type of reaction is encountered in such patients?

Chairman Peterson: I can't answer that question categorically, but such infections are probable. Some of the elderly people with disseminated infection have a reinfection and have got dissemination as a result of the loss of their immunity and/or the depression of their general resistance.

Dr. Downing: Assuming that they have had a benign infection which had gone on to the development of calcified areas in their lungs, demonstrated on previous X-rays, are there any cases on record where those lesions have broken down?

Chairman Peterson: Not that I know of. From what little we know about it, it is very improbable that these lesions will ever break down and that pulmonary calcification, due to histoplasmosis, does not carry with it any risk of further trouble. In fact, it might even be looked for as an insurance against the very slight chance of getting progressive reinfections.

Dr. Downing: What is the general significance and relationship of this work on positive skin tests to histoplasmin and its correlation with X-ray findings to the morbidity of an area where the infection is prevalent?

Chairman Peterson: An attempt to answer this question is at this time pure speculation. We believe that some illness not now clearly recognized may be due to histoplasmosis.

Dr. Downing: In the X-rays you showed, with very numerous calcified lesions scattered throughout the lung, it seems logical to assume that at sometime during the disease, if it's like other granulomatous diseases, there would be some areas of pneumonitis in the area where the calcification is an end result. Apparently, however, X-rays of individuals don't show such lesions. Is this true, or is it just that they haven't been caught at the time that it is present? Have such lesions been seen?

Dr. Furcolow: We have seen areas of pneumonitis in children in relationship to the development of histoplasmin sensitivity, areas which were often entirely asymptomatic, though occasionally they have been associated with definite clinical symptoms, especially where there has been marked regional lymphadenopathy and associated pressure reactions.

Some of the areas of infiltration have the appearance one would expect around a focal granulomatous lesion at the time sensitivity develops. I have a number of photographs of such lesions and will pass these around.

Dr. Downing: Are such lesions common?

Chairman Peterson: They are not common, at least we have not recognized them commonly. The difficulties of establishing proof of the etiology are such that it will be a long time before we can have real confidence in the correctness of such diagnoses individually.

One of the most important aspects of these studies, as they have been carried out to date, has been to re-establish, or at least to re-direct our attention to the fact that tuberculin tests really have significance, that they can be used both in children and in adults to establish the diagnosis of tuberculosis. These studies have also shown that diagnoses of tuberculosis based purely on morphology are not as reliable as they were once thought to be. The tagging of an individual as having tuberculosis purely on the basis of a morphologic lesion, whether it's active, healed or calcifying, is probably not justified.

Dr. H. Bradley, Nashville: There seems to be such a great difference between these nine patients with disseminated infection, how can you feel sure it's the same organism?

Chairman Peterson: The organisms which have been isolated at postmortem examination and during life from both progressive and benign infections have been in so far as we can determine morphologically, culturally and pathogenically identical in all instances. Some minor variations have been noted but not more than is commonly seen in different strains of the same bacterial species. Whether or not the fungus truly forms a single homogenous species without significant variance is a question that we can't answer now.

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Dr. Grant Taylor was to have presented a discussion of Torulosis. He was unable to attend the meeting and we have omitted his discussion.

Round Table Discussion

PRACTICAL AND IMMUNOLOGIC ASPECTS OF PEDIATRIC IMMUNIZATIONS

WALLACE SAKO, M.D., *Chairman, New Orleans, La.*

Chairman Sako: Current trends in pediatric immunizations include earlier immunizations particularly in infancy, the use of multiple antigens to minimize the number of inoculations and to save time, the use of alum or aluminum hydroxide to prolong the antigenic stimulus, and the use of booster doses to maintain high protective levels. The optimal age of immunization, the choice of immunizing agents, the desirability of immunization, and the use of booster doses are governed by various factors and there appears to be no uniform agreement along these lines. It is my purpose to outline briefly the common pediatric immunization procedures with emphasis on newer trends based on recent immunologic studies and to include opinions from my own experience in order to provoke a lively discussion.

PERTUSSIS

Active immunization against pertussis is so highly effective that it has now become an accepted procedure. Since pertussis is antigenically of a single type, it readily lends itself to the production of active immunity provided freshly isolated virulent strains (Phase 1 of Leslie and Gardner) of the whole bacterial cells are used in the preparation of the vaccine. In assessing the few published reports of failures in immunization, we must bear in mind that nonpotent lots of vaccine might be used. This occurs because there is as yet no United States standard of potency. Furthermore, pertussis immunity is never as solid as antitoxic immunity of diphtheria and tetanus. Bacillus parapertussis infection may be so indistinguishable from pertussis that the diagnosis may occasionally be mistaken. Thus failures of prevention under challenge of exposure are to be expected; the disease when contracted, however, is practically always milder.

Pertussis vaccine as it currently appears on the market may be obtained in three forms:

1. Saline suspensions (10 to 40 billions/cc.). For effective immunization, the total number of bacterial cells injected should be from 80 to 120 billion. This should be divided into three doses and administered at three to four week intervals. Weekly intervals which may be used in the presence of an epidemic or likelihood of exposure with rapid production of immunity is not as durable as the monthly interval. The particular concentration to be used depends upon the physician's choice, the higher the concentration the greater the local reaction as a general rule, although young infants tolerate the higher concentrations extremely well.

2. Alum-precipitated vaccine (with or without diphtheria and tetanus toxoids). Immunologic studies show that 30 to 40 billion H. pertussis alum-precipitated cells are just as effective as 80 to 120 billion saline suspended cells. The alum-precipitated vaccine should be administered at monthly intervals. Our own studies show that this product is far superior to the fluid or anhydrox vaccine in the immunization of infants below six months because a higher degree of serologic response is obtained and my impression is that immunity is more durable. To avoid abscess formation when using alum-precipitated vaccine, the material should be injected deep subcutaneously or intramuscularly (as recommended by Bell), with the needle directed distally (as recommended by Sauer), and avoiding intracutaneous inoculation (as recommended by Sako and coworkers).

3. Soluble antigens and endotoxoids are of very little prophylactic value unless whole cells are used in combination.

Until recently it was thought that the young infant could not be effectively immunized against pertussis because of the immaturity of the immune mechanism. Recent studies by various groups of investigators, however, have shown that young infants can be effectively immunized in early infancy when the highest mortality occurs. In the immunization of infants below six months, prolonged antigenic stimulus as afforded by alum-precipitation is necessary for efficient antibody production. The alum-precipitated vaccine, except for its tendency to produce sterile abscesses, gives far less local and systemic reactions that the fluid or combined vaccines. Severe reactions were an infrequent occurrence with the young infants.

Following pertussis immunization, the agglutinins reach a plateau level in two to four months and this level is maintained usually for at least two years. The effect of a "stimulating dose" of pertussis vaccine administered a year or more after the basic immunization is to raise the protective titer to higher levels within a week. A few individuals (perhaps 1% to 2%) can never be made to produce high titers no matter how many inoculations are given. These cases are not necessarily susceptible. Personal observation indicates that agglutinin titers above 1:320 dilution or complement fixation titers of 3 to 4 plus afford solid protection under challenge of intimate exposure. To maintain optimum protection following basic immunization the following alternatives may be used:

1. A stimulating dose of 20 billion cells when exposure occurs or in the presence of an epidemic.
2. Annual stimulating dose of 10 billion saline cells or 5 billion alum-precipitated cells until six years of age.
3. Stimulating doses of above every two years.
4. A stimulating dose of 20 billion saline cells or 10 billion alum-precipitated cells one year after the basic course and the second at six years of age is recommended by Miller.

Smallpox

Calf lymph virus is the product of choice in smallpox vaccination. Vaccination should be performed anytime during the first year of life. Eczema, heat rash, or other widespread skin lesions is a contra-indication. Extreme hot or cold weather is not a desirable period for vaccination. Vaccination after the first year may give rise to severe reactions or complications. The site of choice is the left upper arm at the insertion of the deltoid or higher on the shoulder. Other sites used are the thighs, legs, and the back. The multiple pressure method should be used. I prefer to use a band-aid covering to prevent scratching. Revaccination should be done when the child starts school and again at 12 years of age.

Diphtheria

Basic immunization against diphtheria should be done in the second half-year of life. The alum-precipitated toxoid is the product of choice since it has been conclusively shown that two injections of alum-precipitated toxoid gives a higher and more durable antitoxic immunity than three injections of fluid toxoid. The injections should be given deep subcutaneously or intramuscularly to avoid local reactions and formation of sterile abscesses. The interval between injections should be one to four months. Diphtheria-tetanus toxoid alum-precipitated is the product of choice in conferring basic immunity in infancy and early childhood.

In children above 10 years, the fluid toxoid of Ramon is the product of choice. Since older children and adults may be extremely sensitive to diphtheria protein, sensitivity test (Maloney test) with 1:100 dilution of fluid toxoid intradermally is recommended. If the test is negative three injections of 1 cc. each are administered at monthly intervals. If the sensitivity is great, the dosage is reduced to 0.1 cc., 0.2 cc., 0.3 cc., and 0.5 cc. at monthly intervals.

Recently aluminum hydroxide-adsorbed diphtheria and diphtheria-tetanus toxoid has been found to be highly effective. This product is reported to induce a greater titer of antitoxin, reduce pain on injection, avoid sterile abscesses, decrease the occurrence of persistent nodules, and to reduce general systemic reactions. In my own experience, it is a highly satisfactory product. A protamine-precipitated toxoid is also claimed to be highly effective.

A Schick test should always be performed six months following basic immunization. If positive, the immunization should be repeated. The Schick test should be done again at six years of age and at 12 years of age. The public health physicians would rather give booster injections at these ages. The Schick test should be read in five to seven days unless a control test using heated Schick toxin is done simultaneously, in which case it may be read in two days. An area of discoloration 0.5 cm. or more in diameter denotes a positive test and hence susceptibility. An antitoxic level of 0.03 unit or more/cc. blood is considered as conferring solid protection against diphtheria although a level of 0.004 unit/cc. blood will induce a negative Schick test.

Tetanus

There is no natural immunity to tetanus. Since most of the cases of tetanus encountered in private practice occur from insignificant wounds, the desirability of immunization becomes apparent. The basic immunity can best be conferred with the combined alum-precipitated tetanus and diphtheria toxoid. Studies conclusively show that the alum-precipitated product produces a higher and more

durable immunity than the fluid toxoid. The interval of injection should be one to four months. Miller recommends the aluminum hydroxide-adsorbed tetanus toxoid. An annual booster dose of 0.5 cc. to 1 cc. toxoid is recommended. In case of serious wounds, a booster injection of 1 cc. toxoid should be given. An antitoxic titer of 0.1 unit/cc. blood is generally protective against tetanus.

Typhoid-Paratyphoid

In certain localities, the incidence of typhoid fever is so small that immunization is not necessary. In the South, however, the incidence of typhoid fever is high enough to justify immunization. Mouse protection tests show that young infants are not immune to typhoid. The low incidence in infancy can be attributed to sterile precautions exercised in the preparation of food, formula, and water. I prefer to start immunization in the second half-year of life between or after the immunizations of pertussis, diphtheria and smallpox. Up to three years of age the half dose may be used—0.25 cc., 0.5 cc., 0.5 cc. at one to three week intervals. After three years the full dose of 0.5 cc., 1 cc., 1 cc., should be given. The standard vaccine consists of 1,000 million typhoid and 250 million each of paratyphoid A and B. Annual stimulating doses of 0.1 cc. intracutaneously is recommended (Longfellow & Luippold). The basic immunization should always be given subcutaneously (Luippold).

Combined Toxoids and Vaccines

Recent tendency is for multiple antigens to be combined. Ramon pointed out that mixtures of vaccines and toxoid might be used. Studies show that these mixtures often result in potentiation and prolongation of immunity. Diphtheria toxoid has been combined with tetanus toxoid and pertussis vaccine in the fluid, alum-precipitated, and aluminum hydroxide-adsorbed states. The inclusion of typhoid with the above three antigens gives too severe reactions to be practical.

Influenza A and B Virus Vaccine

A high incidence of reactions in children has discouraged its use. The author has used two doses of 0.25 cc. and 0.25 cc. a week apart with very little reaction and with apparently a great deal of benefit.

Pneumococcus A and B Polysaccharides

Its effectiveness or desirability of administration to children is still to be demonstrated. The author has used the A and B combination in 0.5 cc. doses with the influenza vaccine with slight to moderate reactions.

Various effective schedules of immunization are tabulated on page 725.

Dr. Louis W. Sauer—Evanston, Ill.: Current United States Public Health Service statistics show that over 50% of all pertussis deaths and approximately 5% of those caused by diphtheria occur during the first six months of life. Immunization against both of these diseases should be attempted, therefore, as early as adequate protection can be conferred. Because these deaths are most frequent in institutional infants and in those of the lower economic level, prevention should be attempted as early as possible. With diphtheria immunization clinics well established throughout the country, simultaneous early pertussis and diphtheria immunization warrants attention.

Proof of immunity conferred by the administration of antigens is based on three kinds of evidence: (a) clinical, i.e., by comparison of disease incidence in vaccinated and nonvaccinated controls in the same age range and economic level; (b) serologic, by complement-fixation, agglutination, and opsonocytophagic tests for pertussis; antitoxin concentration levels for diphtheria and tetanus; and (c) skin tests—the positive agglutinogen test for pertussis; the negative Schick test for diphtheria.

Poor Results with Fluid H. Pertussis Vaccine in Early Life

Between 1932 and 1938, commercial fluid H. pertussis vaccine was administered as a routine procedure at the Evanston Health Department clinic, at St. Vincent Infant and Maternity Hospital, and in private practice. At first, three weekly doses of fluid vaccine (10,000 million bacilli/cc.) were administered. In 1936, three weekly doses of 20,000 million bacilli/cc. was tried. Since 1937, the fluid vaccine contains 15,000 million bacilli/cc.; the alum-precipitated, 20,000 million/cc. Prior to 1944, immunization was routinely begun during the seventh month of life because it had been found that the three customary doses of potent vaccine seldom conferred adequate immunity when injected during the first months of life. Approximately 2,000 infants were injected at The Cradle

during the first and second months; and over 1000 infants were injected at Chicago Health Department Infant Welfare Clinics during the third and fourth months of life. By the end of one year pertussis had occurred as frequently in the vaccinated as in the nonvaccinated (control) groups. Various dosages, time intervals, and routes of administration seldom conferred clinical or laboratory evidence of protection. The percent of 3+ or 4+ complement-fixation reactions was lower than

SCHEDULES OF IMMUNIZATION

	Author I	Author II	Miller	Fischer	Conventional procedure
1 mo.	Pert. Alum pptd.				
2 mo.	Pert. Alum pptd.				
3 mo.	Pert. Alum pptd.				Smallpox
4 mo.	Smallpox (1)	Smallpox		Smallpox (1)	
5 mo.	Typhoid			Pertussis	
6 mo.	Typhoid	DPT Plain or	Pertussis	DPT	Pertussis
7 mo.	Typhoid	DPT alum	Pertussis	DPT	Pertussis
8 mo.	Diph-Tet alum pptd.	DPT Precipitated	DPT	Smallpox (2)	Pertussis
9 mo.	Diph-Tet. alum pptd.	Typhoid (3 weekly)		Diph-Tet.	
10 mo.	Smallpox (2)		Smallpox		Diph-Tet.
11 mo.					Diph-Tet.
1 yr.	Tuberculin Test DPT Booster	Tuberculin Test Schick Test	Diph-Tet.	Schick Test	Diph-Tet
15 mo.	Schick Test		Schick-Tet.		
18 mo.			Pertussis		
2 yr.	Tet. booster (annually)	DPT	Tetanus	DPT	Typhoid-Schick
	Typhoid booster annually	Typhoid booster annually			Typhoid-Pert.-Tet.
3 yr.	Pertussis booster	Tet-typhoid booster annually	Tetanus	DPT	
4 yr.					
5 yr.					
6 yr.	Schick-smallpox Pertussis booster	Schick-smallpox DPT	Smallpox-Schick Pert.Tet every 2 years		Smallpox-Schick

when the same dose of fluid vaccine was administered during the second half-year of life. Since 1938, almost all of our infants have been injected with mixtures (fluid or alum-precipitated) of diphtheria toxoid and H. pertussis vaccine, or diphtheria and tetanus toxoids and H. pertussis vaccine.

EARLY COMBINED DIPHTHERIA AND PERTUSSIS IMMUNIZATION

Immediately after Sako reported on "Early Immunization Against Pertussis with Alum-Precipitated Vaccine" at the A.M.A. Meeting in Chicago in 1944 (J.A.M.A. 127:379, 1945), we began earlier administration at the Evanston Health Department clinic and at St. Vincent's. During 1944, three monthly doses (0.5 cc. each) of an alum-precipitated mixture containing double strength diphtheria toxoid and H. pertussis vaccine (30,000 million bacilli/cc.), were administered to 211 infants starting at five months. In 1945 and 1946, the earliest dose was given to 411 infants during the fourth month of life. Follow-up pertussis complement-fixation reactions, diphtheria antitoxin concentration determinations, and Schick test showed that the percent of 3+ or 4+ complement-fixation reactions was lower for the five and four month old groups than when the same dose of antigen was injected after the sixth month of life. Our lowest percent of pertussis protection

occurred in those infants receiving three monthly doses starting at the age of four months. In 1947, when the first dose was administered at three months of life, four monthly doses were used routinely in 238 infants. Any infant who failed to show adequate protection to either pertussis or diphtheria when tested three months after the fourth dose, was given a stimulating (fifth) dose (0.5 cc.) of the alum-precipitated mixed antigens. This almost invariably produced a satisfactory immunity level when the infant was retested a month later. Follow-up data for 1947 show that the percent of adequate protection was higher than when three monthly doses were administered starting at the age of four or five months.

Superiority of Alum-Precipitated Antigens

The infant's immunity response to repeated doses of an antigen is quantitative. It depends upon several factors, such as the potency of the antigen, the time interval between doses, total dose and age when administered. Immunity response of the body (immunization mechanism) is not as well developed during the first months of life as later. Furthermore, comparative studies of fluid and alum-precipitated H. pertussis vaccine (containing half as many total bacilli), injected during the first months of life and later, invariably showed the alum-precipitated antigen to confer a higher percent of immunity response than did fluid H. pertussis vaccine. Its superiority is due, at least partly, to slower elimination whereby the immunizing mechanism has a longer opportunity to elaborate specific antibodies.

In spite of this superiority, alum-precipitated antigens have not come into general use because of occasional alum abscess. Any kind of alum may produce a nodule or cyst at the site of injection. At times it increases in size, becomes fluctuant, drains, and leaves a scar. Various reports have appeared on an administration technic which should decrease or eliminate such severe local reactions. Alternate gluteal areas have been found most satisfactory during the past two years. A 25-gauge ½ to ⅝ inch needle was used. Each dose was terminated by 0.1 cc. of air injected so that most of the alum particles were eliminated from the needle tract. Prompt massage, not too intense, of the site, with dry sterile gauze prevents oozing and distributes the antigens into the deeper tissues. In a total of approximately 2500 injections, alum cyst (discharging abscess) has been almost entirely eliminated by this technic (one abscess). Occasionally a residual induration or circumscribed subcutaneous nodule could be palpated after a month or more. For children over three years of age the deltoid region of alternate arms may be used.

Simultaneous Immunization Against Diphtheria Pertussis and Tetanus

Three monthly or bimonthly doses (0.5 cc. each) of an alum-precipitated mixture of the three antigens were begun during or after the sixth month of life. By the technic described above, alternate gluteal areas were the site of injection. Since 1942, a total of 820 St. Vincent, Wilmette Health Center and private infants were injected with triple alum-precipitated antigens (double strength toxoid of diphtheria and tetanus, 30,000 million H. pertussis/cc.). To date, no child is known to have contracted any of these three diseases; discharging alum abscess is known to have occurred in one instance. In some, a residual nodule could be palpated two months later. Follow-up tests were performed on 98 infants three or more months after the final dose. All of them showed complete immunity to diphtheria (negative Schick Test); 96% to tetanus (antitoxin level of 0.1 unit/cc. serum); and 83% to pertussis (diameter of agglutinogen reaction greater than 10 mm.).

Agglutinogen Skin Test

The agglutinogen skin test has been used at St. Vincent's since 1942, and since 1946 at the Evanston Health Department clinic, as confirmatory evidence of vaccine conferred immunity. Comparison of the pertussis complement-fixation and the agglutinogen test showed good correlation. Likewise diphtheria antitoxin concentration determinations and Schick tests showed excellent correlation. Since January 1947, therefore, pertussis complement-fixation and diphtheria antitoxin concentration tests have been discontinued. At the Health Department clinic and at St. Vincent's, the agglutinogen skin test for pertussis and the Schick test for diphtheria are performed routinely three months after the final (fourth) dose of the mixed alum-precipitated diphtheria and pertussis antigens. One stimulating dose of the alum-precipitated mixture is administered whenever the tests, read 24 hours later, show inadequate protection.

Neither the A.M.A. Council on Pharmacy and Chemistry nor the National Institute of Health

has released this valuable reagent. Confirmatory clinical evidence is still necessary to show that the positive test connotes immunity; the negative test, susceptibility to pertussis. Although we, too, have no evidence proving immunity of infants with positive agglutinogen tests after vaccine administration, the following two instances warrant reporting. At St. Vincent's in 1942, an infant was placed in a four-crib isolation room containing three infants who had been admitted a few days previously. That night the nurse reported that the newest arrival had severe pertussis-like paroxysms. The coughing infant was promptly transferred. The cough plate was positive. The three exposed infants were immediately injected at three-day intervals with H. pertussis vaccine (1., 2 and 3 cc. 15,000 million/cc.); none developed pertussis. Months later, one was transferred to another floor where preliminary agglutinogen skin tests were being performed. Unlike that of any of the other infants an area of induration on this infant measured more than 30 mm. in diameter 24 hours later. The other instance occurred at the Evanston clinic in October 1947. Follow-up agglutinogen and Schick tests were performed on a group of 28 infants who had their first dose of alum-precipitated mixture at the age of three months and were being tested three months after the final (fourth) dose of antigen. On the following day, when the readings were performed, all showed negative Schick tests; and in all but three the agglutinogen induration was greater than 10 mm. in diameter (i.e., immune to pertussis). In two of the three, the induration was less than 10 mm. in diameter; in one, there was no reaction. Upon questioning the mother, it was found that this child, now two years old, had been injected not at our clinic, but by a private physician who had administered three weekly doses of fluid vaccine starting at the age of four months. To the two who showed partial immunity, one stimulating dose of the mixed alum-precipitated antigen was administered; to the latter showing no pertussis immunity, three monthly doses will be given, and these three children will be retested later. The follow-up agglutinogen skin test has been performed on a total of 742 infants.

Summary

Four monthly doses of an alum-precipitated mixture of diphtheria toxoid and H. pertussis vaccine administered after the third or fourth month of life should confer immunity to diphtheria and pertussis.

Three monthly or bimonthly doses of an alum-precipitated "triple" mixture of diphtheria toxoid, H. pertussis vaccine, and tetanus toxoid administered after the sixth month of life should confer immunity to diphtheria, pertussis, and tetanus.

Alternate gluteal regions are the sites of choice for alum-precipitated antigens in children under three years.

When performed three months or more after the final dose of mixed alum-precipitated antigens the positive pertussis agglutinogen skin test and the negative Schick test for diphtheria were adequate evidence of immunity.

Before a previously immunized child attends kindergarten or school, one stimulating dose of alum-precipitated mixed antigen is recommended.

Probable exposure to a disease of a previously immunized child warrants very prompt administration of one stimulating dose of the respective fluid antigen.

Dr. Francis A. Garbade—Galveston, Tex.: The first thing we should do with patients when they are about three or four months of age is to discuss immunization with the parents, what to do and why, and how to go about it. In this discussion we mention the results that can be expected from immunization. It is very important that the reactions they can expect from the various immunization procedures be explained. There are a few precautions that will minimize the reactions when used with some of the preparations, particularly from alum toxoids. All the biologicals should be kept in the refrigerator at the proper temperature. We keep them in the refrigerator until immediately before giving them to the child and in so doing we have minimized a great many reactions. Needles and syringes should be boiled and sterilized in distilled water and dry syringes and dry needles, having no water in them at the time of immunization, used. Give all immunization injections deep in the muscle, not subcutaneously.

Our first immunization is for smallpox, and this should be given usually between three and six months of age. There are several reasons for giving it at this time. Smallpox, chickenpox, whooping cough and typhoid fever occur more frequently in small infants because they have practically no immunity. We use the multiple puncture method for smallpox vaccination. The site of vaccination should be the deltoid area, because perhaps there is less chance of getting an

infection in this area. We never immunize a child against smallpox with any type of skin eruption, or when he has an upper respiratory infection.

We start whooping cough immunization usually between four and six months of age, and use one of two preparations, either the alum-precipitated combined toxoid in doses of 0.2 and 0.5 cc. at intervals of one month, or one of the saline preparations in 40 billion/cc., given in 0.5, 1.0 and 1.5 cc. at intervals of one month. The reactions have been minimal. The infant may have a slight fever for 24 to 36 hours and a sore arm during that time. A piece of aspirin, depending on the age of the child, can be given about three hours after the injection, and repeated every three to four hours if necessary. We give a booster dose of whooping cough vaccine at least once a year, or at any time the child is exposed.

We give combined diphtheria tetanus immunization beginning at the age of eight or nine months, using three injections at intervals of one month. We use alum-precipitated toxoids for the smaller infant. For older children we use fluid toxoid. Reactions have been minimal. Occasionally there is a reaction, and it occurs usually when the injection has not been given deep enough in the muscle. Only once in 14 years have we had an abscess from using an alum-precipitated toxoid. We do a Schick test from three to six months after the last injection. We give a booster dose of tetanus once a year afterward, and I believe from the recent reports that it is worth while to give booster doses of diphtheria toxoid. Once a year we give one injection of combined diphtheria, pertussis and tetanus toxoid. We repeat the Schick test every two years and before the child goes to school. Smallpox revaccination is done every five to seven years. We have given typhoid vaccine and in Galveston, as in New Orleans, typhoid is necessary because we, too, are subject to tropical infections and our water supply may be in danger at any time. We give typhoid vaccine during the second year because most infants are fed from clean utensils, and sterile bottles, and milk is boiled during the first two years of life. We give a booster dose of typhoid vaccine at least once a year in the spring before children go swimming or to camp.

With reference to influenza viral vaccine we have endeavored to give it to those children who have repeated, frequent, severe upper respiratory infection. In a series of about 40 children to whom this vaccine was given last year, the number and severity of respiratory infections were lessened. The dose that we gave was 0.25 cc. and a week later 0.25 cc. again.

It is better to allow a child to have modified measles by giving either placental extract or preferably gamma-globulin. In order to modify measles we give the 2.0 cc. injection four to six days after a first exposure, deep in the buttocks.

With reference to whooping cough, there are two preparations which are useful. The first is a hyperpertussis, which if given immediately, particularly if it is given within two weeks after exposure, is of some value. Another preparation is Lederle's antigen given in 2.0 cc. doses every day for five days. The protection is not always effective and the children do get some reaction from it. It is our duty to see that as many children are immunized against infective diseases as possible and by following a simple plan of immunization, immunizing particularly against smallpox, pertussis, diphtheria, tetanus, typhoid and influenza in certain cases, we can improve the health of children in our respective communities.

Dr. Bret Ratner—New York: I have the impression that the immunologic process requires about one month or longer to manifest itself in the blood. There is no good reason why one should keep to any strict time schedule so long as we do not crowd the injections. From the allergic standpoint all the large doses could be obviated if it were proven experimentally that giving much smaller doses would produce a better immunity. I wonder whether we should not stretch the number of injections from three to six, seven or eight smaller doses. The recall reactions will make these small injections produce a higher ultimate titer. That has been the experience with diphtheria. The question of antibodies formed in the young infant is very important. When I suggested that the fetus could be sensitized in utero to foods and to the substances which the mother ingested, most immunologists said that no young infants nor fetus could develop antibodies. Our experiments with guinea pigs prove that newborn guinea pigs could develop antibodies. They require a little longer time and their antibody formation is not as efficient as in older children, but certainly the work by Dr. Sako on pertussis indicates pretty conclusively that young children can develop antibodies. The mechanism for antibody production is there or otherwise they probably would not survive. The question Dr. Sauer raised about there being no diphtheria is true, I suppose, for the younger age group, but young adults are coming down with diphtheria. We ought not to be too sanguine about

accepting nonexistent diphtheria and we should give as many repeat doses as possible to the young adolescent.

The use of alum-precipitated toxoid has been a very difficult thing for me to accept. Why can't we use fluid toxoid in smaller doses in greater numbers?

I would like to suggest the use of adrenalin with each and every injection of toxoid or vaccine in office practice. In this way one can avoid unusual reactions that might be otherwise very serious. There is no contraindication to using adrenalin. I have spoken to several immunologists and they have told me that they believed that the adrenalin produced enough blanching actually to serve the dual purpose of avoiding anaphylaxis and also reducing the speed with which the material gets into the system, so that in a sense it delays the absorption.

I would like to mention the use of 3% picric acid in alcohol for smallpox vaccinations. The procedure is very simple. After the vesicle has formed the picric acid in alcohol is painted on the vesicle each day until it hardens. It reduces many of the secondary infections and produces a very small scar.

I would like Dr. Sako to answer a question about one problem of typhoid immunization. We have been using four intracutaneous injections of 0.05, 0.1, 0.15 and 0.2 cc. intracutaneously rather than subcutaneously. Dr. Garbade suggested the use of aspirin and every patient who is immunized against typhoid in our office is given 0.3 gm. aspirin when he leaves the office, and I have never seen any systemic reaction.

I am very glad to hear the enthusiastic remarks about influenza vaccine because we have just finished a study of 200 children, who were given 0.1 cc. of influenza viral vaccine intracutaneously with no reaction whatsoever in any of them. We give two doses. The allergic reaction from the newer influenza viral vaccine is markedly minimized by centrifugation and precipitation. I would like to suggest that when you give any viral vaccine do a skin test with the vaccine. If you get a systemic reaction to the vaccine, the patient will show a marked reaction. If he does not, you go right ahead with the injection. Use undiluted vaccine as you get it from the bottle and inject enough to make a little bleb. Then watch the patient for 10 or 15 minutes and if there is no reaction, go ahead and give the immunization. In that way you will spot that one extraordinary case that might have died from egg white sensitivity.

I would like to bring up the question of the agglutinin test. I do not understand it, because it is apparently a delayed 24-hour reaction and means, as far as I can interpret it, a hypersensitivity rather than an immunity. It is very much like the tuberculin test. Of course, it may not be. It just seems that what we are getting in a positive agglutinin test is a sensitization reaction and not an immunity, although there may be actually an immunity factor there.

Chairman Sako: In answer to Dr. Ratner's question about the use of intradermal typhoid vaccine, I think that immunization can be done effectively, in order to minimize the reaction as you mentioned or to eliminate a certain degree of protection without reaction might be more desirable than a greater degree of immunity with reaction.

About the question of parapertussis vaccine, this can be used and is recommended generally, but until more published reports are available as to the comparative incidence of parapertussis and pertussis we cannot know whether this should be incorporated in the pertussis vaccine.

German measles is mild and, therefore, I have not given any gamma-globulin for prophylaxis. However, where a pregnant mother has received gamma-globulin it does help in the prophylaxis. I have given four ampules of gamma-globulin to a mother in the first three months of pregnancy as recommended.

Dr. J. V. Greenbaum—Cincinnati: Will you say something about scarlet fever immunization?

Chairman Sako: As far as my experience goes there is a high incidence of reaction both in the Dick toxin and to the tannic acid preparation. The protection against scarlet fever is purely antitoxic and does not prevent antibacterial infection. It may give one a false sense of security to immunize against Str. hemolyticus of scarlet fever. The high incidence of reactions and the comparative mildness of the disease in the South and the effective agents which we have for therapy more or less discourage its use. When tannic acid material was first brought out, Dr. Gaylord Anderson asked me to immunize his children. After they arrived in Minneapolis, they developed scarlet fever of a rather severe sort. Dr. Anderson, therefore, felt that the immunization against scarlet fever in his personal experience was not very satisfactory. The published figures of its effectiveness is largely confined to medical students and nurses. I think it is all well and good if for those

who are continually exposed to scarlet fever. But I can truthfully say that I received inoculations against scarlet fever as a medical student myself, and I felt mighty sick after the doses.

Question: What is your opinion of the intradermal scarlet fever immunization?

Chairman Sako: I have not used it.

Question about rabies vaccine.

Chairman Sako: You have to use the material which is available and the community where I practiced had a Pasteur center and I am obligated to them. It is one of the nasty things—probably the path of least resistance is the best.

Question: "Do you get very much reaction in young infants from alum-precipitated pertussis toxoid?"

Chairman Sako: No, I have had very little. The whole secret is in giving the injection deeply and intramuscularly. Also, as Dr. Sauer has brought out, an injection of a little air incorporated makes it clear the tract of the material.

Dr. Ratner: Dr. Sako, that question of alum versus fluid toxoids would be interesting to answer.

Chairman Sako: I have not had much trouble with the alum-precipitated material. In a year and a half I have not had a single abscess formed. I must admit that the products must be more highly refined and the diphtheria-tetanus alum-precipitated toxoid is more satisfactory. You have got to think of the public health importance of two injections versus three. That is a public health proposition that enters into a mass campaign.

Dr. J. W. Britton—Foley, Ala.: I would like to ask Dr. Garbade if he gets proper immunity when the toxoids are given deep intramuscularly?

Dr. Garbade: We have a very low percentage of positive Schick tests after the procedure and the immunity does last longer by using alum-precipitate preparations. However, when a child is brought in with an injury requiring an immediate booster dose of tetanus toxoid, we use fluid toxoid because there is a more rapid absorption of the fluid toxoid.

Dr. Britton: Do you believe that you do not get too rapid absorption by the intramuscular route to get good immunity?

Dr. Garbade: No, we get good immunity, but it takes longer to build it up and it lasts longer.

Dr. W. L. Chadwick—Denver, Colo.: Have you had any experience with intradermal whooping cough vaccine, particularly in the first three months of life? We are doing some work at the medical school in Denver and I would like to find out about experience elsewhere.

Chairman Sako: Psychiatrists have stated that all these inoculations might be detrimental upon the infant from the psychiatric standpoint. The first year of life the child does not usually remember sufficiently to be frightened, but if you start giving the child two years old typhoid vaccine you will have a problem even to get him in your office. It is highly desirable to impress upon mothers that booster doses are necessary in all these immunizations following a basic immunization. In arranging your schedule for immunizations, it is necessary to give an injection about every month for the first 10 months of life.

Question: Have the mothers objected to this?

Chairman Sako: They like it. They come back every month to check up, and they feel at least they get something when they come. The Board of Health in Louisiana has circulated pamphlets urging early immunization. They ask for it. Whooping cough immunization is a must.

Dr. Frauenberger—Evanston, Ill.: Just a remark about the psychologic aspect. It is important for every pediatrician and doctor to give a psychologic test before giving these immunizations. It takes only a second or two to explain honestly and sensibly just what the procedure is going to be, and then go ahead and give it. If the child cries, have one of these minted candies handy to pop into his mouth. He usually stops crying and you do not have trouble afterwards.

Pediatrics

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SPECIAL FEATURE SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

EDWARDS A. PARK, M.D., *Editor*, PAUL HARPER, M.D., *Associate*

Statements appearing in this column do not necessarily reflect the opinion of the editors nor are they to be interpreted as the official opinion of the Academy.

INTRODUCTION

OUR attention has been called to two corrections which should be made in the letter of Dr. Thomas O. Gamble as it appeared in this column in the September issue of PEDIATRICS. Dr. Gamble writes:

"On page 365 I quoted the first objective of the Association of American Physicians and Surgeons. Quotation marks should have been placed at the end of the two sentences which are enclosed in parentheses. Anyone reading my letter might assume that the last two sentences represented my interpretation of the first objective. So, while I agree entirely with the objective and its interpretation, I should not be given credit for something which belongs to the A.A.P.S."

The second correction is made in the letter from Dr. William J. Orr, Buffalo, New York, which is published below.

Dr. Myron E. Wegman and Dr. Ralph V. Platou, Professor and Head, Department of Pediatrics, respectively of Louisiana State University of Medicine and Tulane University School of Medicine have polled the professors of pediatrics throughout the country to ascertain their experience with federal funds. The results of this survey are summarized in their letter.

September 25, 1948

DEAR DR. PARK:

I would like to correct an error made by Dr. Thomas O. Gamble in his letter published in the September issue of PEDIATRICS. In his communication Dr. Gamble states, "At the annual meeting of the New York State Medical Society held in May 1948, an effort was made to secure the Society's endorsement of the Committee's program. I am happy to report that the House of Delegates sensed the hidden dangers of the proposal and refused endorsement." That statement is incorrect. I introduced the resolution before

the House of Delegates and no vote was taken on the resolution. The action taken was a vote to refer the resolution to the Council of the State Society for their consideration. I refer you to the minutes of the meeting as published on pages 99 and 100 in the September 1, 1948 edition of the New York State *Journal of Medicine*. I would also like to state that the resolution was approved by the Reference Committee of the Society and recommended for adoption. This is published in the minutes on pages 97 and 98 of the same issue.

(Signed) WILLIAM J. ORR

October 20, 1948

DEAR DR. PARK:

Much of the discussion regarding the proposals of the Committee on Improvement of Child Health that federal aid be provided for pediatric education has centered around the desirability of embarking on an entirely new program. Since both the undersigned have administered federal funds related to our departmental activities, we thought it worthwhile to determine the experiences and reaction to the use of such funds of other professors of pediatrics throughout the country.

Accordingly, on August 15, 1948, the following letter was sent to the heads of departments of pediatrics at the 70 medical schools in the United States. This letter is reproduced in its entirety:

"It has occurred to two of us who are intimately engaged in the teaching of pediatrics, Ralph Platou, Professor at Tulane, and myself, that it would be helpful to the fellows and officers of the Academy of Pediatrics to have a summary of the experiences of pediatric departments with federal funds.

"We shall appreciate it if you will indicate your answers to the following questions:

1. I have (have not) administered grants from governmental agencies related to my teaching or research.

2. Our grants have come

(a) directly from the federal agencies ——.

(b) through a state agency ——.

(c) through both routes ——.

3. There has (has not) been interference or attempt to direct the use of the grant along lines which I did not approve.

4. Our general experiences with federal grants here in the department of pediatrics have been Satisfactory ——. Unsatisfactory ——.

"Since we presume that you have transmitted any opinions on the I.C.H. proposal to Dr. Wilson or Dr. Hubbard, this questionnaire does not seek suggestions but merely a summary of our collective experiences with federal funds. We shall, nevertheless, appreciate any supplementary remarks you wish to make. An extra copy of this letter which need not be returned, is enclosed.

"It is our intention to summarize the results without identifying any individual, and to send each of you a copy of this tabulation as soon as possible.

MYRON E. WEGMAN, M.D.
Professor of Pediatrics
Louisiana State University
School of Medicine"

Replies have been received from all 70 schools and the results may be presented as follows:

1. Twenty-nine, 41%, of the professors stated that they had administered federal funds. Thus federal aid to pediatric departments cannot be considered a new program.

2. Those who had experience with federal funds reported the following methods by which the funds had been received.

(a) Directly from the federal agencies	12
(b) Through a state agency	6
(c) Through both routes	11

3. and 4. In every instance the professors who have had federal funds to administer indicated in their answers to questions (3) and (4) that there had been no interference or attempt to direct the use of the funds along lines which the professor did not approve, and that in every instance the general experience had been satisfactory.

While, as is clear from the letter, no direct attempt was made to secure further discussion, a few spontaneous comments were added concerning these relationships. Two of the professors were clear cut in their statements that without federal aid it would be extremely difficulty, if not impossible, to carry on their programs. Three others were emphatic that not only had there been no interference but there had been great aid in securing objectives. A quotation from one letter is in order:

"My own experiences, with both the Children's Bureau and the United States Public Health Service, have been wholly satisfactory. In all instances, these federal agencies have shown themselves to be reliable public servants, interested in making sure: 1. that the money granted us was spent for the purposes outlined, and 2. that we met adequate standards of performance. Naturally we have no complaint about these two qualifications."

On the other side of the picture there was one professor who intimated that while in general his experience had been satisfactory there was room for improvement in methods and details of administration. One department head made the point that the biggest disadvantage he saw to federal funds at the moment was the need for annual renewal. He would prefer grants for a longer period of time, say five years.

Three comments from those who answered Question 1. negatively are of interest. One stated that his medical school was receiving a large grant of federal funds for aid in postgraduate education, including pediatrics, but that he had nothing to do with the administration of these funds and considered this situation very unsatisfactory. Another wrote, "We want nothing to do with federal money." From another school came the statement, "Have had no grants of any kind for pediatrics and need them badly. Our experience with other grants from the federal government has been excellent."

One should not conclude from these data, of course, that relations are necessarily perfect between university departments of pediatrics and those who are responsible for the distribution of federal funds or that funds are given without any restriction. It does seem clear, however, that the experiences of department heads have been such that it is only fair to expect that problems which do arise can be solved successfully and that the basic integrity of the medical schools in administering their own programs may be satisfactorily safeguarded.

(Signed) MYRON E. WEGMAN
(Signed) RALPH V. PLATOU

TRENDS

IN HEALTH LEGISLATION AND ADMINISTRATION

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

A NEWLY appointed Advisory Committee on Maternal and Child Health and Crippled Children's Services met with the Children's Bureau in Washington, September 14 and 15, 1948. This Committee consisted of the following members:

Raymond B. Allen, M.D., President, University of Washington; Harriett M. Bartlett, Associate Professor of Social Economy, School of Social Work, Simmons College; Allan M. Butler, M.D., Professor of Pediatrics, Harvard Medical School; W. W. Bauer, M.D., Director, Bureau of Health Education, American Medical Association; George Bugbee, Executive Director, American Hospital Association; Dean A. Clark, M.D., Director, Health Insurance Plan of Greater New York; Hazel Corbin, R.N., General Director, Maternity Center Association; William J. Darby, M.D., Departments of Medicine and Biochemistry, School of Medicine, Vanderbilt University; M. Edward Davis, M.D., Professor of Obstetrics and Gynecology, School of Medicine, University of Chicago; Claudia Durham, R.N., Associate Professor of Nursing, Meharry Medical College; Kenneth E. Easlick, D.D.S., Professor of Dentistry, School of Dentistry, University of Michigan; Nicholson J. Eastman, M.D., Professor of Obstetrics, School of Medicine, The Johns Hopkins University; Mrs. Lulu Evanson, Director of Education, North Dakota Farmers Union; Katharine Faville, R.N., Dean, College of Nursing, Wayne University; William T. Green, M.D., Professor of Orthopedic Surgery, Children's Hospital, Boston; Charles F. Good, M.D., Directing Supervisor, Health Service, Board of Education; Harry H. Gordon, M.D., Professor of Pediatrics, School of Medicine, University of Colorado; John P. Hubbard, M.D., Director, Committee for the Improvement of Child Health, American Academy of Pediatrics; Herbert R. Kobes, M.D., Director, Division of Services for Crippled Children, University of Illinois; Lawrence J. Linck, Executive Director, The National Society for Crippled Children and Adults; William Mengert, M.D., Professor of Obstetrics and Gynecology, Southwestern Medical College, Dallas; James Raglan Miller, M.D., Trustee, American Medical Association; Oscar L. Miller, M.D., Orthopedic Surgeon, The Miller Orthopaedic Clinic; Mary Blanche Moss, Executive Secretary, The American Association of Medical Social Workers; Ewell Newman, Social Case Work Consultant, National Urban League; Harry A. Ong, M.D., American Academy of Pediatrics; John Z. Preston, M.D., General medical practice; Harry Read, Executive Assistant to the Secretary-Treasurer, Congress of Industrial Organizations; Duncan E. Reid, Professor of Obstetrics, Harvard Medical School; Raymond Rich, Chairman, Raymond Rich Associates; Hugh B. Robins, M.D., Director, Calhoun County Health Department; Edward S. Rogers, M.D., Dean, School of Public Health, University of California; Catherine E. Sheckler, R.N., Assistant Professor, Nursing Education, University of Chicago; Nathan Sinai, Dr. PH., Professor of Public Health, School of Public Health, University of Michigan; Thomas E. Shaffer, M.D., School Physician, The University School, Ohio State University; Randel Shake, Director, National Child Welfare Division, The American Legion; Ernest Stebbins, M.D., Director, School of Hygiene and Public Health, The Johns Hopkins University; Florence C. Thorne, Director of Research, American Federation of Labor; Felix J. Underwood, M.D., Executive Officer, Mississippi State Board of Health; Abram L. Van Horn, M.D., Medical Director, Kate Macy Ladd Fund; R. M. Walls, D.D.S., Dental practitioner; Mrs. Roy C. F. Weagly, President, Associated Women, American Farm Bureau Federation; James L. Wilson, M.D., Professor, Department of Pediatrics and Communicable Diseases, School of Medicine, University of Michigan;

Barbara White, Educational Secretary, The American Physiotherapy Association; Mrs. Eva Ylvisaker, Chief Dietitian, Children's Hospital, Cincinnati.

One interesting feature of the make-up of this list is the fact that it includes broad representation, both of nonprofessional as well as professional groups. As was true also of the National Health Assembly, the list includes those who speak for the consumers of medical care, as well as those who are concerned with giving it. Included in the Committee are representatives of the National Farmers' Union, The American Farm Bureau Federation, CIO and the American Federation of Labor.

This Committee elected as its Chairman, Dr. Harry H. Gordon, Professor of Pediatrics, School of Medicine, University of Colorado. During the two days of this first meeting the time was devoted mostly to general discussion and review of the activities of the Children's Bureau. Subsequent meetings, which are planned to be held about twice a year, may be expected to bring forth definitive statements and recommendations. The subsequent meetings will be reported in this column as they occur. The organization and function of the Children's Bureau are reviewed here, therefore, to serve as general background.

In welcoming the Committee, Dr. Martha Eliot stated. "The Congress has laid down broad rules within which federal aid can be given. Within that area, the Children's Bureau must make many policy decisions as to which services are most needed; how they can be provided effectively; what help health workers and agencies need in providing services. On such questions as these we want the benefit of your counsel as to what is in the best interest of mothers and children. The door is wide open to you, as spokesman for the purveyors and consumers of health services, to tell us what we ought to do and how we ought to move—always within the authority given us by the Congress."

The organization and function of the Bureau were reviewed by several members of its staff. A Division of Research in Child Development, under the direction of Dr. Katherine Bain, conducts investigations, develops standards of care and provides information and consultation. This involves collaboration with and services to other bureau divisions and such agencies as the Department of Agriculture, Office of Education, Army Quartermaster Corps and the National Research Council, as well as many private agencies and state and local public agencies.

The Mental Health Unit, under the direction of Dr. Henry H. Work, Jr., "fosters wider understanding of mental health, stimulates development and improvement of mental-health services for children in child health and welfare programs supported by public or private funds, promotes development of diagnostic and treatment resources for children with personality and behavior problems and for mentally retarded children, and provides consultative service."

The Division of Health Services is responsible for the administration of grants to States for maternal and child health services and for services for crippled children and for the EMIC program. For the administration of these programs the Division maintains eight regional offices throughout the country. Dr. Edwin F. Daily, the Director of this Division, reviewed the increase in sums made available by Congress for health services and the present activities of his Division. He stated, "In 1936, $3,800,000 were made available annually for federal grants for maternal and child health services, or $1.70 per live birth. In 1948, this amount had increased to $11,000,000, or $2.60 per live birth. In 1936, $2,850,000 were available annually for federal grants for services to crippled children, or $.06 per child under 21 years of age. In 1948, this had increased to $7,500,000, of $.16 per child under 21 years of age. The increases in the appropriations,

however, have barely kept up with the increased cost of salaries, supplies, and hospital care; the number of children cared for could not increase proportionately to the increased appropriations."

This Division, which now administers $18,500,000 a year for maternal and child health services and for services to crippled children, has a staff of 71, including those in the central and eight regional offices.

Dr. Daily further pointed out that in 1935 before the passage of the Social Security Act only 23 state health departments had programs for maternal and child health services. Now all of the states have divisions of maternal and child health and crippled children's services. In addition to the allotment of federal and state funds to county or local health departments for maternal and child health services, the state health agency, through its division of maternal and child health provides consultatives and supervisory services on the medical, dental, nursing, nutrition, and health-education phases of the maternal and child health program. Postgraduate courses in obstetrics and pediatrics are held for practicing physicians, and institutes and training courses are held for public-health nurses and other health workers. Stipends are provided for staff workers in state and local health departments to enable them to take additional professional training.

Under the program for crippled children, grants are made to state crippled children's agencies to provide medical, surgical, corrective, and other services and care for children who are crippled or who are suffering from conditions that lead to crippling, and to provide facilities for diagnosis, hospitalization, and aftercare for such children.

Additional activities of the Division of Health Services include the completion of care under the EMIC program for cases authorized before the fiscal year 1948.

The Social Service Division, under the direction of Miss Mildred Arnold, is responsible for promoting services directed toward improving the social well-being of all children and the protection and care of dependent, delinquent, neglected, and handicapped children, including the administration of grants to states for child-welfare services.

The Division of Statistical Research, under the direction of Mr. Edward E. Schwartz, collects and analyzes for administrative use and for public information, statistics on Children's Bureau programs in the fields of material and child health and child welfare. This Division is responsible also for statistical research in the social, economic and health aspects of child life.

The Division of Reports, under the direction of Miss Mary Taylor, is responsible for the writing and distribution of popular leaflets, pamphlets and special feature materials. This Division publishes the Bureau's monthly periodical, "The Child."

SPECIAL REVIEWS

JOSEPH STOKES, JR., M.D., *Editor*

HYPOCALCEMIC STATES

By KATHARINE DODD, M.D.
Cincinnati, Ohio

THE subject of hypocalcemic states is one on which a great deal of work has been done but one in which there is as yet much disagreement concerning some points and a recognized lack of knowledge of others. In general it may be stated that hypocalcemic states are manifested clinically by signs and symptoms of tetany. The symptom complex of tetany is now less common than in former times when rachitic tetany was the most frequent cause of convulsions in infancy. It was well described in the older literature.[1] The manifestations consist of central and peripheral nervous system symptoms, irritability often alternating with lethargy, nystagmus and strabismus, contractions and pain in the muscles of the face with "half moon eyes," "carp mouth," trismus and convulsions. Edema, most marked in the hands, feet and around the eyes is often observed. Confirmatory signs of tetany may be elicited by special methods of examination. Chvostek's sign, jerking of the facial muscles when the facial nerve is tapped, is a sign of tetany in children from one month to two years of age. It is unreliable in newborn infants, in older children and adults since in them it may be present normally. When the facial muscles are in spasm with manifest tetany it can seldom be elicited. The peroneal sign consists of dorsiflexion and abduction of the foot on tapping the peroneal nerve on the lateral surface of the fibula just before the knee. Trousseau's sign is carpopedal spasm induced by pressure applied for some time over the upper arm or leg. Erb's sign, or increased electrical excitability of the peripheral nerves to the galvanic current, was the most reliable proof of tetany in the days before blood chemical analyses were available. The procurement of electrical reactions is such a time consuming procedure that they are seldom sought for now. Involvement of the autonomic nervous system has not been stressed in recent years as a manifestation of tetany but was well known to the older writers. They recognized as part of the picture of spasmophilia of infants disturbances of respiration; irregularity, tachypnea, an asthmatic type of breathing apparently due to bronchial spasm and even respiratory arrest as well as the better known laryngeal stridor. Bradycardia, or more rarely tachycardia, and cardiac murmurs were noted. Disturbance of the tonus of the gastrointestinal tract, manifested by abdominal distention, constipation or diarrhea, pylorospasm and vomiting were seen. Pallor, erythema and urticaria were attributed to spasm of the capillaries of the skin. As a further possible sign of tetany, hemorrhages producing bloody vomitus, melena and hematuria should be mentioned. While hemorrhages are seldom described in patients with tetany, animal experiments[2,3] have demonstrated that a hemorrhagic diathesis may exist both in parathyroidectomized animals and those with hypocalcemia from a diet very low in calcium.

From the Children's Hospital and the College of Medicine, University of Cincinnati, Cincinnati, Ohio.

Read in part at the Eastern Areal Meeting of the American Academy of Pediatrics, Buffalo, N.Y., April 29-30, 1948.

Twenty-seven years ago, when my pediatric experience started, the finding of hypocalcemic tetany associated with rickets was an every day experience, particularly in the late winter and spring. Tetany occurred mostly in artificially fed infants but breast fed infants, particularly Negro infants, prematures and twins, were not immune. The almost universal irradiation of milk, or the addition of some form of vitamin D to milk, and the wide-spread adoption of the addition of vitamin supplements to infants' diets have made the observation of rachitic tetany more rare. Nevertheless it still may be seen and should always be thought of when an infant between the ages of six weeks and one year is hyperirritable, has convulsions, spasms and pain in the extremities or any of the other signs of tetany. We have seen two cases of rachitic tetany in fast growing premature infants recently at the Cincinnati Children's Hospital. Although both had received some vitamin D, the amount had not been sufficient considering their prematurity and rapid growth. When I was in Boston a year ago twins with rachitic tetany were demonstrated at one of the clinical conferences. Clinical and radiologic signs of rickets may be present in these infants but often they show little or no clinical signs, except craniotabes, and the roentgenologic findings are apt to be inconclusive. The typical chemical findings of low serum calcium, normal or low phosphorus and increased alkaline phosphatase may be necessary to substantiate the diagnosis of rachitic tetany.

Hypocalcemic tetany is occasionally seen in children with celiac disease, cystic fibrosis of the pancreas or other conditions where absorption from the gastrointestinal tract is poor. The tetany may be caused either by failure to absorb vitamin D or failure to absorb calcium. The more general use of fat soluble vitamins in finely dispersed droplets which can apparently be adequately absorbed by these children should decrease the incidence of this complication where the absorption of vitamin D is at fault.

Although rachitic tetany is not usually associated with disease elsewhere in the body it was recognized by earlier writers that both respiratory and gastrointestinal diseases might be complicated by tetany. Powers[4] found hypocalcemia in some children with pertussis and convulsions, as we have subsequently. Some of the rachitic tetany we used to see became manifest with either respiratory or gastrointestinal disease.

Parathyroid tetany following thyroidectomy and due either to disturbance in parathyroid function or inadvertent removal of the parathyroid glands is common in adults but rare in children. Spontaneous hypoparathyroidism occurs in children as well as in adults. Cases have been reported by Drake and others[5] and we have one patient at the Children's Hospital, an irritable, somewhat mentally retarded boy, who has convulsions whenever he has fever. He has the usual chemical findings of parathyroid tetany, a low serum calcium, high phosphorus and normal phosphatase activity. Medication with calcium and dihydrotachysterol has improved his disposition and decreased his susceptibility to convulsions.

At the Cincinnati Children's Hospital we have recently been interested in three syndromes where hypocalcemia occurs. All are found in infants and all are characterized by convulsions, vomiting and a tendency to edema. The peripheral signs of tetany in these infants are apt not to be conspicuous but they have signs of central and autonomic nervous system involvement. The three types of the hypocalcemic syndrome we call neonatal tetany, post-acidotic tetany and hyperventilation tetany.

Neonatal tetany was first described in 1913 by Kehrer,[6] an obstetrician. He reported six cases of newborn infants with spasms accompanied by edema, vomiting or fever in which therapy with calcium chloride was dramatically effective. Shannon[7] and Bass

and Karelitz[8] redescribed the syndrome and reported the finding of hypocalcemia in the disease. In 1937 Bakwin[9,10] described three more cases with determinations of serum calcium, phosphorus and phosphatase. The calcium was low, the phosphorus tended to be high, but in contradistinction to rachitic tetany and similar to parathyroid tetany the phosphatase was normal. Bakwin demonstrated that a fall in calcium and a rise in phosphorus with production of tetanic symptoms could be produced by the administration of phosphates to newborn infants. He proposed the theory that transient hypoparathyroidism, secondary either to immaturity of the parathyroid glands or possibly to hemorrhage into the parathyroids, is common in the newborn period. Snelling[11] in 1943 reported 11 more cases but thought the tetany was caused by permanent or temporary impairment of kidney function with consequent retention of phosphorus. Two infants with severe congenital kidney disease were only temporarily benefited by giving fluid and calcium gluconate intravenously. All the other children recovered in a few days on the same therapy.

In the last 10 years we have observed 33 instances of a hypocalcemic syndrome of the newborn at the Cincinnati Children's Hospital with persistent vomiting, convulsions and edema as outspoken symptoms. In the first seven years of this period only five cases were seen, in the last three years when interest was focussed on tetany 28 cases were observed. The onset of symptoms was from the first day of life until the 13th. Edema and vomiting were seen commonly with an early onset, convulsions occurred both early and late.

A typical case history is presented. T. C., a full term infant was born by low forceps breech extraction, but breathed well. When put to breast he vomited after each feeding. The stools were normal. On the 6th day of life he became irritable and a tremor of hands and feet developed. On the 9th day of life he had 5 generalized convulsions. On admission to the hospital the next day he was alert but irritable. The face, hands and feet were edematous. The deep reflexes were increased and ankle clonus was present. The serum calcium was 7.6, the phosphorus 8 mg./100 cc. blood, the alkaline phosphatase 8 Bodansky units. He was treated with $CaCl_2$ with dramatic cessation of vomiting, irritability and convulsions, and disappearance of edema. Two days after admission the levels of both calcium and phosphorus were normal.

Vomiting, convulsions and edema were the chief manifestations of tetany in all 33 patients. Chvostek's sign was usually present when sought for, peripheral nervous manifestations were conspicuous by their rarity. Hemorrhagic manifestations were not uncommon. Since newborn infants often bleed because of anoxemia or birth trauma, the hemorrhages may have predisposed to hypocalcemia rather than have been caused by it. It may be of interest to note that two of the infants with hypocalcemia had erythroblastosis and one was the child of a diabetic mother. Perhaps hypocalcemia may be a not uncommon complication of other neonatal disturbances of infants.

In the series of 33 patients all the serum calcium values were less than 9 mg./100 cc. blood, about ¼ less than 7, ½ between 7 and 8 and ¼ between 8 and 9. The serum phosphorus was above 8 in 10 of the 25 tests run. The phosphatase was normal in all but one infant who had erythroblastosis. These findings of low calcium, high phosphorus and normal phosphatase are compatible with Bakwin's idea that tetany of the newborn is caused by immaturity of the parathyroid glands.

The second form of hypocalcemia commonly seen in Cincinnati infants we call post-acidotic tetany.[12] Many infants after recovery from diarrhea, dehydration and acidosis suddenly show alarming symptoms of collapse with ashen skin and cold extremities,

edema, coffee ground vomitus, twitchings of the muscles and even convulsions, or respiratory arrest. On careful examination unevenness of breathing may be noted. There may be bradycardia or tachycardia, flushing or pallor. The symptoms of such infants suggest tetany. When they are given calcium salts, calcium gluconate by the intravenous route when the symptoms are severe, $CaCl_2$ by mouth when less severe, a prompt improvement in their symptoms often ensues.

The following case history is typical. G. U., a 4-month-old infant had diarrhea for 2 weeks. On admission to the hospital he was extremely dehydrated and breathing rapidly. Blood CO_2 content was 7.8 mEq. He was immediately given intravenous fluid therapy, his acidosis corrected with sodium bicarbonate solution and all feedings discontinued. On the second day in the hospital the child looked greatly improved, his hydration was much better, his color was good and his diarrhea had ceased. But by evening generalized clonic convulsions developed associated with nystagmoid movements of the eyes, jerky respirations, a poor color and abdominal distention. The CO_2 content of his blood was now 25.4 mEq. so that he was no longer acidotic. His serum was only 6.2 mg./100 cc. blood. Two grams of $CaCl_2$ were administered by gavage and 25 minutes later the tremors of the limbs subsided, the respirations became regular and the color improved. In 3 hours poor respirations, nystagmoid movements of the eyes and clonic movements of the extremities recurred. Again all untoward signs disappeared after the administration of 2 gm. of $CaCl_2$. The infant was maintained on calcium therapy in doses of 3 gm. for 5 days and was discharged well shortly thereafter.

Table I illustrates in six cases a fall in calcium and phosphorus such as has been observed in 55 infants with somewhat similar stories. At the time of appearance of symptoms the serum calcium of 51 of the 55 infants was below 9, in 24 it was below 8, and in 16 below 7 mg./100 cc. blood.

As may be seen in the table when the patients were studied in the early acidotic phase of the diarrhea the calcium and phosphorus were normal. With recovery from the acidosis and cessation of diarrhea, the calcium value fell, once as much as 4.1 mg. and once as low as 6.8/100 cc. A similar fall occurred in the phosphorus. We believe that during acidosis calcium is mobilized from the skeleton and lost by way of the urine and

TABLE I

CHEMICAL CHANGES IN PLASMA DURING POST-ACIDOTIC PERIOD

Patient	HCO_3 mEq /l	Ca mg./100 cc.	P mg./100 cc.	Phosphatase B. units	State of Patient
T.R.	7.4	11.1	5.3	13.4	Acid
	29.3	8.1	2.3	8.1	Post-acid
F.	4.6	—	6.5	9.1	Acid
	24.8	6.8	2.7	5.0	Post-acid
D.B.	11.4	11.2	5.5	8.0	Acid
	22.6	8.8	3.8	3.5	Post-acid
G.A.	15.6	10.5	7.7	5.2	Acid
	27.0	7.0	2.6	2.7	Post-acid
H.R.	13.6	11.2	—	4.8	Acid
	26.6	7.1	2.6	2.7	Post-acid
J.D.	20.4	9.4	4.1	4.4	Acid
	26.1	8.0	2.1	2.8	Post-acid

feces. When acidosis is corrected, calcium and phosphorus are rapidly deposited in the bones, the baby becomes hypocalcemic and tetany develops. Calcium medication is needed to tide him over his difficulty until his balance again becomes stabilized.

The third form of hypocalcemia with tetanic manifestations is that seen with hyperventilation. Some of the children have apparently had reflex stimulation of their respiratory center due to slight respiratory infection. Some have been small infants who have been treated with acetylsalicylic acid. Respirations become deep and pauseless, the children lose water from their lungs, the temperature rises very high and convulsions and other signs of tetany appear. Two case histories will illustrate the point.

P. H., a 9-month-old infant, developed an upper respiratory infection 5 days before admission. Two nights before admission he cried continuously; the next night he began to hyperventilate. His temperature rose to 41.1° C. On admission he was dehydrated and acutely ill. The high electrolyte concentration of his blood showed that he had lost a great deal of water. The serum calcium was 7.2 mg./100 cc. blood. After hydration was accomplished with large amounts of glucose in water, his temperature fell to normal but his serum calcium fell to 5.4 mg./100 cc. blood. He became cyanotic and began to convulse. Sedatives and calcium gluconate were given by vein and calcium chloride by mouth. Gradually his condition improved, the hyperventilation ceased, the color returned to normal, the convulsions stopped and he began to notice his surroundings. He was discharged well in 8 days.

The second patient, J. A., a 5-month-old infant, had fever and vomiting for 5 days before admission and finally one day of diarrhea. During his illness he was given powders containing salicylate every 3 hours. His mother noticed that he was breathing deeply. His eyes crossed and his muscles began to twitch. The temperature on admission to the hospital was 40.0° C. The baby was dehydrated and irritable, he was hyperventilating and convulsing at times. Chemical examination of the blood showed that the infant had lost a great deal of water. His serum chloride was high, 124 mEq./100 cc. blood, NPN was very high, 102 mg./100 cc., he was slightly acidotic with a low pH, low CO_2 content and low CO_2 tension. Salicylate level was 55 mg./100 cc. blood; the serum calcium was 7.4 mg./100 cc. The baby was treated with large amounts of 5% glucose in water, some sodium bicarbonate to facilitate excretion of salicylate, and large doses of calcium chloride by mouth. Gradually the clinical picture changed. The hyperventilation stopped, dehydration was overcome, blood NPN fell and the convulsions ceased. A second determination of the serum calcium on the fourth day showed that it had returned to normal.

In Table II are presented figures of the serum chemistry of five infants with hyperventilation. The pH is normal or high, the CO_2 content low, the chloride and NPN

TABLE II

CHEMICAL DATA ON INFANTS WITH HYPERVENTILATION SYNDROME

Case	pH	CO_2 mEq./l	Cl mEq/l	Ca mg./100 cc. blood	NPN mg. %
Kl.	7.48	18.8	151.6	6.4	113
Ki.	7.38	6.3	119.0	7.2	58
Je.	7.37	11.0	104.0	6.6	78
Ha.	7.33	14.3	115.6	7.7	72
Ho.	7.36	11.6	122.0	8.6	107
Ge.	7.55	17.3	120.0	6.6	56

high indicating hyperventilation with loss of water and hyperelectrolytemia. The serum calciums are all low.

The mechanism of the hypocalcemia of prolonged hyperventilation with accompanying loss of water from the body is not clear. It may be that prolonged hyperventilation per

se lowers the serum calcium or there may be some renal factor connected with the extreme hyperelectrolytemia and lack of water for excretion by the kidneys which leads to lowering of the calcium in the blood.

That hypocalcemia is not always associated with tetany is well known. Children with nephrosis, chronic nephritis and pneumonia may have low levels of serum calcium yet usually have no signs of tetany. The depression of serum calcium has been correlated with depression of the serum protein, and the failure of most of the children to show signs of tetany explained on the assumptions that it is the calcium which is bound to the protein rather than the ionized calcium which is depressed. That this is not the whole explanation is shown by the fact that the levels of serum calcium and those of protein often bear no relation to each other. As an example I should like to cite one child with nephrosis whom we have on our wards at present. His serum calcium varies from 6 mg. to 11 mg./100 cc. blood with no change in his consistently low serum protein and no signs of tetany at any time.

The reason why tetany appears at one level of serum calcium and not at another is not well understood. The serum pH is one determining factor. It is known that with low serum pH even extreme degrees of hypocalcemia are not attended by signs of tetany. A reciprocal relation between serum values of calcium and phosphorus has impressed many observers. Nevertheless, there is no critical level of calcium at which tetany invariably appears. We have seen tetany in patients with a serum calcium of 9mg./100 cc. blood and, as in the child with nephrosis, found it absent at 6 mg. The literature on patients with hypoparathyroidism presents many such examples. Since tetany is an expression of dysfunction of the neuromuscular system which is affected by a variety of factors, dissociation between the level of calcium and response of the neuromuscular system is understandable.

When signs and symptoms of tetany occur in hypocalcemic states, calcium therapy usually brings about dramatic improvement of the patient. For emergency treatment we use 0.5 to 1 gm. of calcium gluconate in 2% solution given by vein and for sustained treatment 1 to 2 gm. of calcium chloride diluted with saline or the child's formula to a 2% solution and given by mouth. Calcium chloride which has an acidifying action is the only calcium salt which can be relied upon for oral therapy. Since the effect of calcium salts is only temporary, a running order for calcium chloride to be given every 8 to 12 hours is necessary. One gram a day is usually sufficient for a premature infant, 2 to 3 gm. for an older infant. The dose should be cut in half after the first two or three days to avoid the development of severe acidosis. A few words should be said about the dangers of calcium therapy. Intravenous therapy often produces tachycardia and when given rapidly may result in respiratory arrest. In gravely debilitated patients necrotic lesions at the site of injection have occurred with slow intravenous infusion. Intramuscular injection of calcium gluconate is inadvisable as it may cause necrosis and the formation of abscesses. Concentrated solutions of calcium chloride may damage the gastric mucosa. Dilute solutions of calcium chloride have caused no damage in our patients.

Since tetany is only a symptom, the underlying cause of the hypocalcemia must always be considered. Children suffering from rachitic tetany will need large doses of vitamin D. Hypocalcemia of the newborn is usually transient, as it should be if the cause is immaturity of the parathyroid glands. Post-acidotic tetany occurs when the child is recovering from his dehydration and acidosis. In hyperventilation tetany hydration of the body and reestablishment of kidney function by the administration of large amounts of water

is always necessary. In rachitic tetany and many cases of tetany of the newborn calcium therapy is often dramatic and brings about prompt cessation of all symptoms. In post-acidotic and hyperventilation tetany many functions of the body are upset as well as those affected by hypocalcemia. The administration of calcium is a useful part of therapy but if the child is to recover all aspects of his illness must be considered and adequately treated.

I have presented a discussion of a subject of great interest to pediatricians of a generation ago which I believe is now due for reevaluation. A broadening of the symptomatology of tetany beyond the description in current American text books has lead to increased recognition of hypocalcemic states and intelligent and successful management of many cases. But a great deal more has to be learned about the subject before we can accurately evaluate just what part hypocalcemia alone plays in the production of many of the symptoms we see in hypocalcemic states, what prevents the appearance of symptoms of tetany in some hypocalcemic states, and what brings about hypocalcemia. A review a few years hence will probably have to cover a great deal more ground than I have covered.

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Elland and Bethesda

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

LEONA BAUMGARTNER, M.D., *Contributing Editor*

THE TEACHERS BECOME THE STUDENTS

For a three weeks' period during the month of June 1948, the University of Illinois, through its Division of Services for Crippled Children, and the U. S. Children's Bureau conducted an institute for professors of medical social work in the approved schools of medical social work. The objectives of this institute were several: one was to give to the teaching group in one of the important professional fields ancillary to medicine an opportunity to review the contributions of its field to the public medical care programs, particularly those in maternal and child health and services for crippled children; another was to aid in the critical recruiting activity which needs to be carried on in order to staff the public health programs adequately with this type of personnel; a third was to stimulate thinking regarding the make-up of the curriculum for medical social students in order to include in the teaching program an adequate orientation and training in the activities of the public health programs.

The institute consisted of a group of leaders in the various aspects of maternal and child health and crippled children's programs conducting discussions concerning their individual aspects of the program. A state health officer, Dr. W. L. Treuting of Louisiana, reviewed the total health program. Dr. Herbert R. Kobes, Director of Services for Crippled Children in Illinois, and Dr. Edwin F. Daily of the U. S. Children's Bureau discussed the medical care, particularly the crippled children's, programs as they are found throughout the nation. Miss Helen F. Dunn, Director of the Division of Public Health Nursing in the Department of Health and Welfare of the State of Maine, presented the contributions of the public health nurse to the full program in public health. Miss Hedwig B. Trauba of the Illinois Services for Crippled Children and Miss Gertrude M. Church, Regional Nursing Consultant of the U. S. Children's Bureau, aided in the discussion of this phase covering, in particular, the nurses' work in the medical care programs. Miss Zoe Hall of the Illinois Services for Crippled Children, Miss Edith L. Baker, Miss Ruth Olson and Miss Doris Siegel of the U. S. Children's Bureau presented the medical social aspects of the public health programs. Miss Dora Goldstine of the University of Chicago School of Social Service Administration assisted in preparation of material and discussion in this phase of the total program. These discussions occupied the first week of the institute which was held in Chicago, Illinois.

The second week the students spent in states throughout the country observing the work of the public health departments, especially as to the service rendered by medical social workers and how their activities correlate with those of the other members of the departments.

During the third week of the institute, which was again held in Chicago, the students and faculty reviewed the observations gathered on the field study. Along with the material that was presented during the first week the group determined that there was need for spreading wider through the profession a knowledge of the work done in the public medical programs. Many comments were made concerning the high grade of care which was given to children through the state programs. It was felt that, as soon as they might be consistent with university policies, changes in the curriculum should be made which would make it possible to train medical social workers more adequately to undertake full responsibilities in the various aspects of their field of work. Emphasis had previously been given to the work of the medical social workers in hospitals and it was felt that now sufficient emphasis should also be given to the work which needs to be carried out in the health department programs.

The institute was considered by all to be highly successful and the teaching method used could probably be extended to other fields. Among these would be an activity which could bring together the professors of pediatrics in the approved medical schools. This group has an intense interest in the public health and social aspects of the practice of pediatrics and thus would probably welcome an opportunity to gain more first-hand information concerning the public health programs as they

relate to pediatrics. One advantage of the institute, as it was held in June is that there was practically complete representation of the top people in a teaching field. A group which would include a number of individuals greater than approximately 30 would probably be too large, and benefits from several similar sessions would not be equivalent to those deriving from a single session representing all of the medical schools. There is a possibility that, through the educational funds which the Children's Bureau might be able to grant to one of the states, an institute similar to that for the medical social workers could be set up for the professors of pediatrics.

The device of having the people who are teachers serve as the student body and having the faculty composed of people who devote their efforts to practical aspects of a problem worked with eminent success in this institute and merits further consideration by other teaching groups.

HERBERT R. KOBES, M.D., *Director*
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Springfield, Ill.

INCIDENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES

NUMBER OF REPORTED CASES OF 9 COMMUNICABLE DISEASES IN THE UNITED STATES DURING THE 4-WEEK PERIOD SEPTEMBER 12–OCTOBER 9, 1948, THE NUMBER FOR THE CORRESPONDING PERIOD IN 1947, AND THE MEDIAN NUMBER OF CASES REPORTED FOR THE CORRESPONDING PERIOD, 1943–47

Division	Current period	1947	5-year median	Current period	1947	5-year median	Current period	1947	5-year median
	Diphtheria			Influenza[1]			Measles		
United States	922	991	1,387	4,859	3,595	3,595	3,081	2,298	2,403
New England	37	21	25	2	6	16	149	118	229
Middle Atlantic	50	56	77	16	13	19	529	386	386
East North Central	60	79	143	37	95	95	467	521	455
West North Central	41	94	99	25	9	22	130	237	69
South Atlantic	342	329	329	1,703	1,552	1,013	221	324	220
East South Central	221	167	264	84	116	110	99	40	50
West South Central	97	137	178	2,699	1,632	1,950	479	236	146
Mountain	54	46	46	217	137	179	257	118	169
Pacific	20	62	126	76	35	43	400	318	340
	Meningococcus meningitis			Poliomyelitis			Scarlet fever		
United States	167	177	359	6,185	3,243	3,243	2,40	2,248	4,810
New England	9	6	22	110	249	249	198	202	306
Middle Atlantic	31	30	78	914	774	774	372	401	663
East North Central	34	29	72	1,198	1,361	906	588	506	1,087
West North Central	12	16	41	1,374	210	343	217	195	447
South Atlantic	22	22	46	661	287	258	301	261	770
East South Central	16	24	28	213	101	112	338	188	370
West South Central	18	33	31	271	37	216	122	104	152
Mountain	8	5	10	145	84	172	78	145	179
Pacific	17	12	44	1,308	140	275	266	246	550
	Smallpox			Typhoid and paratyphoid fever			Whooping cough		
United States	3	2	11	367	467	605	3,509	12,227	8,184
New England	0	0	0	13	23	29	349	1,172	886
Middle Atlantic	0	0	0	45	50	71	1,004	2,622	1,953
East North Central	1	0	7	48	62	62	657	3,431	2,587
West North Central	0	1	1	24	37	33	130	756	409
South Atlantic	0	0	1	65	98	113	445	1,517	1,108
East South Central	2	1	1	54	66	79	196	320	303
West South Central	0	0	1	52	66	90	307	1,116	655
Mountain	0	0	0	29	24	41	159	588	358
Pacific	0	0	0	37	41	30	262	705	610

[1] Massachusetts, New York, North Carolina and Pennsylvania excluded; New York City and Philadelphia included.

For total United States	Cases for each week of current period				For total United States	Cases for each week of current period			
	1st	2nd	3rd	4th		1st	2nd	3rd	4th
Diphtheria	199	186	252	285	Poliomyelitis	1,841	1,609	1,527	1,208
Influenza	926	1,117	1,323	1,493	Scarlet fever	447	585	665	783
Measles	709	728	780	864	Smallpox	2	1	0	3
Meningococcus meningitis	36	37	38	46	Typhoid and paratyphoid fever	105	95	96	72
					Whooping cough	1,023	872	843	771

Data furnished by the Division of Public Health Methods, United States Public Health Service.

NEWS AND ANNOUNCEMENTS

Status of Pediatrics in the United States Army

Pediatricians who served in the armed forces during the war will be interested to learn that pediatrics as a specialty has been given recognition by the Army Medical Corps. With the inauguration of residency training in army general hospitals it became apparent that pediatric experience was essential to adequate training in almost all specialties.

One aspect of this program, important to all pediatricians, is that in the event of another mobilization the consultants who have been appointed to the Surgeon General in pediatrics will have a strong voice in the adequate utilization and assignment of pediatricians.

Four regular army medical officers have been certified by the American Board of Pediatrics. They have been given the responsibility of directing pediatric training in army general hospitals. To assist and supervise residency training, over 350 outstanding specialists have been appointed by the Secretary of War as attending staff for general hospitals continuing residency training. The following pediatricians have been appointed:

Harry A. Towsley, James L. Wilson, and H. Sidney Heersma—Percy Jones General Hospital; Harold K. Faber, Edward Campion, and Francis Scott Smyth—Letterman General Hospital; Sidney R. Kaliski and Russell Blattner—Brooke General Hospital; Harry H. Gordon—Fitzsimons General Hospital; Arthur H. Hurd—McCornack General Hospital; Walter B. Seelye—Madigan General Hospital; Philip A. Mulherin—Oliver General Hospital; Donald C. Marshall—Tripler General Hospital; A. Horst Agerty and Nathan H. Einhorn—Valley Forge General Hospital; William A. Howard and John A. Washington—Walter Reed General Hospital; Harold D. Warren, Station Hospital, Ft. Jay, N.Y.; Russell B. Scobie—U. S. Military Academy, West Point, N.Y.; Edmund N. Joyner, III—Army Area Consultant—First Army Area; Norman Kennall—Tilton General Hospital; and Charles Rennick—William Beaumont General Hospital.

These experienced teachers provide expert consultation, supervision, and active teaching of the residents. The attending and assigned staff in other specialties assist in the care of pediatric patients and assist in the training of pediatric residents. The residents appointed for pediatric training in army general hospitals are young officers of the regular Army Medical Corps who express a desire for such training. Army interns also rotate through the pediatric section as do residents in internal medicine.

The Army has always provided medical care to dependents of military personnel within the capabilities of its medical installations. Such care has long been recognized as an important morale factor. Children were ordinarily cared for in the out-patient clinics. There were no real separate pediatric departments. During the past few years pediatric sections have been built up in those general hospitals at present conducting residency training. The pediatric section of Brooke General Hospital, San Antonio, Texas and Walter Reed General Hospital in Washington, D.C. have reached standards satisfactory for residency training in pediatrics. They have been recommended for approval by the Council on Education of the American Medical Association.

Temporary approval of Brooke General Hospital has been granted by the American Board of Pediatrics. The pediatric sections of both these hospitals each see over 10,000 out-patients, over 1,000 in-patients, and 1,200 newborns each year.

* * *

Lendon Snedeker, M.D., on October 1 became Assistant Administrator at the Children's Medical Center, Children's Hospital, Boston. He is now concerned with the problems and planning that go with the development of the Center.

* * *

Among the three recipients of the 1948 Roosevelt Medals, presented by the Theodore Roosevelt Association, is Mrs. Rustin McIntosh, Dean of Barnard College. The Association's citation called her, "a brilliant educator, the successful and beloved head of a great school," who sought to train the whole personality of her pupils and said that to her child training also implied parent training.

* * *

The Rochester Child Health Institute announces two assistantships of one year each; one beginning the first of January and one the first of July of each year.

These services include preventive medicine in pediatrics with the opportunity of studying normal growth and development, care of the newborn, well child care, psychologic problems in young children and school examinations. These are equivalent to fellowships in the sense that opportunities for both service and research are given.

The stipend of $1620 is offered to suitable candidates. The first available fellowship will be January 1, 1950.

INTERNATIONAL NEWS AND REPORTS

Vanderbilt University School of Medicine announces that Professor Arvid Wallgren, of Stockholm, Sweden, will be the next Abraham Flexner lecturer. Professor Wallgren will arrive in the United States about March 1, 1949.

The original announcement of this Lectureship was made in the fall of 1927 when Mr. Bernard Flexner, of New York City, gave $50,000 to Vanderbilt University for the purpose of establishing the Abraham Flexner Lectureship in the School of Medicine. This Lectureship is awarded every two years to a scientist of outstanding attainment who shall spend as much as two months in residence in association with either a department of a fundamental science or of a clinical branch.

Professor Wallgren has been Associate Professor of Internal Medicine at Uppsala University and Head of Pediatrics at the Royal Caroline Medical Institute since 1942. He is an honorary member of the American Academy of Pediatrics; Canadian Society for the Study of Diseases of Children; Argentine Pediatric Society; German Pediatric Society. He is co-editor of Acta Paediatrica and a member of the Editorial Board of Annales Pediatrici; Pediatria Danubiana; Acta Tuberculosea; Archiv für Kinderheilkunde. He is president of the Swedish Association for Children's Welfare; the Swedish Red Cross Committee on Tuberculosis; the National League Against Tuberculosis; the Save the Children Fund; and Counseiller to the State Board of Public Health.

He is widely known in Europe and the United States for his pediatric writings which include over 200 papers in the field of pediatrics and child health.

BOOK REVIEWS

Skin Manifestations of Internal Disorders (Dermadromes). Kurt Wiener, M.D. $12.50, 661 pages, 386 illustrations and 6 color plates. C. V. Mosby Company, St. Louis, Mo., 1947.

This book represents the most recent attempt to provide a systematic description of the skin manifestations of internal disorders. The author has coined and used throughout the volume the term "dermadrome" to designate the dermal component of a syndrome. Thus for instance the characteristic exanthem is the "dermadrome" of scarlet fever, erythema multiforme and skin nodules the "dermadromes" of rheumatic fever.

The dermatologic symptoms are detailed under the heading of the various diseases. This facilitates reference within the text for those not conversant with all the intricacies of dermatologic classification.

Author and publisher have done a commendable job in presenting the material in clear and readable form. A profusion of excellent photographic illustrations enhances and amplifies the text. A few handy reference tables are found at the end of the volume. The listing of bibliographic references at the bottom of the page where the work is cited should tend to promote a more comprehensive study of various topics. The author's style of writing, however, is occasionally not as clear as might be desired.

The subject matter is well covered from the viewpoint of infectious diseases and of those conditions which pertain more properly to adult individuals. There are some important deficiencies which impair the utility of this volume for physicians primarily interested in diseases of children. Such important subjects as the skin manifestations of allergy and of the nutritional disturbances in infancy are entirely omitted because, as the author states, "excellent modern monographs on these subjects are available." Other conditions of pediatric interest such as scleredema, epidermolysis bullosa and the like are not included, presumably because they are not an expression of systemic disease.

Sporadic references to the dermal manifestations of internal disorders are found in the literature. The author has attempted to bring all of these signs and symptoms together in one volume. However the end result, this reviewer feels, is a summary of dermatology which differs from others primarily in the form of presentation of the subject matter.

P. A. di Sant'Agnese

Psychiatric Examination of the School Child. By Muriel Barton Hall. $4.50, 368 pages, The Williams & Wilkins Co., Baltimore, 1947.

This book, designed primarily for the medical practitioner, is intended to portray general psychiatric principles which the author's experience has shown to be useful in the clinical examination of the school child from five to 17 years of age. It is not intended to be a textbook in child psychiatry. The material is so organized, however, that it gives a good idea of what happens in a child psychiatry clinic when a child is referred for a psychiatric opinion. More important, it makes specific suggestions and describes methods of investigation which the physician can make use of in his practice. The author, a psychiatrist in Liverpool, England, has had experience in a child guidance clinic, a psychiatric clinic, a children's hospital, and a health department, and she has been able to watch the progress and development of many children over a period of from five to 10 years.

The introduction (Chapter I) gives a brief history of the development of child psychiatry. Part One (Chapters II to V, pp. 10-79) discusses investigative methods, beginning with the significance of the complaint, running through the technic of interviewing, history taking, the psychologic, physical, and psychiatric examination of the child, and ending with a consideration of record keeping.

Part Two (Chapters V to XIII, pp. 80-315) takes up a discussion of the common specific behavior disorders. The author is well aware both of the limitation in usefulness of descriptive "diagnoses" and of the difficulty one meets in attempting to devise a workable classification of

children's behavior disorders, but in writing a book some kind of an outline has to be followed and the one used in this book well suits its practical, clinical purpose. First, disorders relating to mental development are discussed: mental deficiency; educational problems of the dull, average, and superior child; and specific disabilities. Second, physical disorders are taken up under the headings of general bodily ill-health, physical defects and deformities, anomalies of growth, endocrine disorders, psychosomatic disorders, and disorders affecting brain and central nervous system. Third, a chapter each is devoted to habit problems, behavior disorders, juvenile delinquency, psychoneurotic syndromes, psychoses in childhood, and psychopathic states.

Part Three (Chapters XIII and XIV, pp. 316-356) discusses briefly types of treatment used in child psychiatry, reports and recommendations, and legal procedures observed in England. There is a general bibliography at the end.

The style of the book is formal but readable. Both theory and technical language have been held to a minimum and case illustrations abound. It is the reviewer's feeling, therefore, that the book can serve as an introduction to child psychiatry and that the physician who reads it will not only acquire a background of information which will help him in his practice and in his relationship to school and health activities, but he will also have a practical viewpoint upon which he can develop his knowledge of the dynamics of human behavior, his technic of interviewing, and his ability to handle the everyday emotional disturbances of parent and child which he sees in his practice.

HALE F. SHIRLEY

TRAITE DE DIETITIQUE DU NOURRISSON By Maurice Lust, 539 pages, Masson et Cie, 120 Boulevard Saint-Germain, Paris VI. 1947.

This volume on infant feeding contains chapters on the criteria of nutrition (physical and behavioral growth, relation between weight and height, physical peculiarities of the infant, etc.); breast milk and breast feeding; artificial feeding, including analyses of various species of milk, and of milk substitutes, and of various supplemental foods; vitamins and minerals; the modifications of milk; the technics of feeding; diet lists; and the feeding of premature and debilitated infants. In general, the outline parallels rather closely that of Jeans and Marriott's "Infant Nutrition" (fourth edition).

Perhaps the chief interest of Dr. Lust's book to the American reader lies in a comparison of present-day French practice with American. Breast feeding is advised up to the age of 9 to 12 months, although it is admitted that only a few mothers will continue it so long, and weaning is done very gradually, over a period of months. Incidentally, the reviewer found no reference to wet-nursing, a practice which Americans are apt to think of as common in France. The addition of supplemental foods is later than is now the general American practice: cereal at 4½ to five months, vegetable soup in small amounts not earlier than six months; fruit purees at nine months; egg at nine to 12 months, and meat at about 18 months. In comparison with the trend in this country to place babies on three-meal schedules at increasingly early ages, French practice as outlined here is to give five feedings at six months, four at nine months, and five again at one year and later. The self-demand schedule is not mentioned; on the contrary, the necessity for regularly scheduled feedings is stated. The daily amount of milk from nine months on is given as 600 gm., less than common American practice.

For the general American pediatrician this volume will be of little value. For teacher or investigator, the bibliography which occupies 42 pages may be decidedly useful, but the absence of an index (other than a table of contents) will make utilization of the text difficult. Actually, there appears to be little of any material in it that is not covered, often more satisfactorily, in American texts.

HAROLD K. FABER

LETTERS TO THE EDITOR

Re: Toxoplasmic Encephalomyelitis, Gabriel A. Schwarz, et al., PEDIATRICS 1:478, 1948.

September 8, 1948

Dear Dr. McCulloch:

In our paper on Toxoplasmosis, recently published in PEDIATRICS, we included a case reported by Drs. Syverton and Slavin in the "Probable" cases in our table on page 488. Dr. Syverton has protested the inclusion of his case in the "Probable" group. The reason his case had been included in probable cases was simply because of his own uncertainty, and consequently ours, as to the relationship of the infecting agent and the symptomatology which the patient presented. Since we are stressing the clinical side, it was our feeling that this case should be clinically considered as a "Probable" case rather than a proven case.

Actually, Dr. Syverton's and Slavin's case is scientifically substantiated as a true case of human toxoplasmosis. The only thing that puzzles us about his case is whether the infection was the cause of the symptoms which the patient had.

Sincerely yours,

(signed) GABRIEL A. SCHWARZ, M.D.

* * *

Re: Multiple Cystic Tuberculosis of the Bones, McLemore Birdsong, M.D., and Camillus S. L'Engle, Jr., PEDIATRICS 1:767, 1948.

July 21, 1948

Dear Doctor McCulloch:

The report by Birdsong and L'Engle in the June issue of PEDIATRICS, leaves me unconvinced.

It is difficult to explain the finding of tubercule bacilli by the authors. One would like verification by guinea pig inoculation. This would seem a desirable check, since, peculiar for tuberculosis that was not as yet terminal or overwhelming (tuberculous meningitis), the tuberculin skin test was negative.

The reproductions of the X-ray films of skull and pelvis are strikingly similar to those of the Hand-Schüller-Christian, Letterer-Siwe disease. I do not believe the absence of foam cells in the biopsy rules out xanthomatosis. Our experience has been that foam cells may be found in the middle-aged lesion, that the early lesion is usually a cluster of endothelial cells (endothelioma) and the older lesion may be sclerosing and hemorrhagic.

The age of the patient, the leukocytosis and fever, favor xanthomatosis of the Letterer-Siwe type. The negative tuberculin skin test makes one question the finding of tubercule bacilli.

It should be recalled that Hand's first report considered tuberculosis as the etiology for the syndrome now bearing his name. Hand's second report corrected this initial impression.

In view of the response of xanthomatous lesions to radiation therapy, I believe the case warrants trial of such treatment, even though the prognosis of Letterer-Siwe disease is not so favorable as Hand-Schüller xanthomatosis or eosinophile granuloma.

Very truly yours,

(signed) FRANCIS SCOTT SMYTH, M.D.

AUTHOR'S REPLY

August 4, 1948

Dear Dr. McCulloch:

Your letter of July 26 was received and I will be glad to reply to Dr. Smyth's letter.

For your own enlightenment, we have reviewed the slides on this case and not only were the organisms found, but on two occasions about six months apart the biopsy showed typical pathologic changes of tuberculosis. The negative tuberculin that we experienced in this child can be explained on an overwhelming infection in that the child was quite toxic in the hospital and died within a couple of weeks after being discharged.

Very sincerely yours,

(signed) MCLEMORE BIRDSONG, M.D.

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